DOCTORAL THESIS

What are the optimal methods for reducing blood loss in hip and knee arthroplasty

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Abstract

This Master of Science by Research thesis explores blood management strategies regarding hip and knee joint replacement surgery.

I begin my work by exploring the background to why this is important, with a history of transfusion and joint replacement surgery.

I then examine the evidence behind blood management strategies in arthroplasty and identify areas where the evidence is lacking.

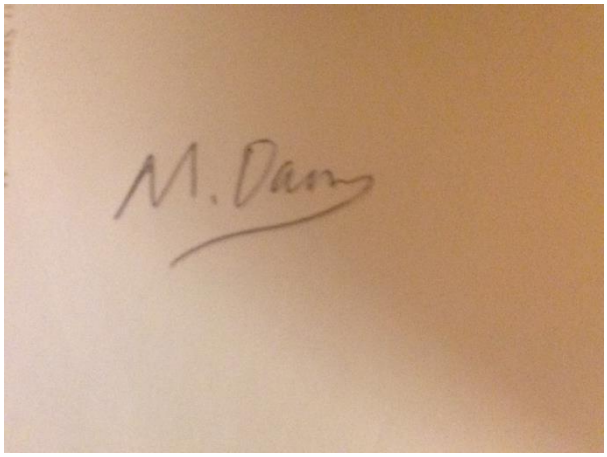
I present my two papers published and accepted for publication.

I finish with a discussion of the limitations and what I learnt from my work.

Including in the appendix is work I was involved in regarding blood management in joint replacement surgery but this was not my own original work so was not included within the main section of this text.

Declaration- Original work statement

This thesis is submitted to Bond University in fulfilment of the requirements of the degree of Masters by Research. This thesis represents my own original work towards this research degree and contains no material which has been previously submitted for a degree or diploma at this University or any other institution, except where due acknowledgement is made



Dr Michael Dan

Acknowledgements and Dedication

I dedicate this work to my family, especially my wife Tyler, whose love and support gives me the confidence to set goals and strive to achieve them.

To Dr Ray Randle and in particular Dr David Liu. Thank you for giving me the opportunity to be involved in research and a solid grounding in orthopaedics. I strive to one day be as good a clinician to my patients and well respected by my colleagues as you. Thank you for your patience, guidance and support.

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Table of contents

BACKGROUND

Total joint arthroplasty is the operation of choice and a reliable option for end stage arthritis of the hip and knee. With a growing and aging population, the incidence of total hip and knee arthroplasty is increasing. According to the Australian National Joint registry, there was a 4.1% increase in total knee arthroplasty (TKA) performed in 2012 compared to 2011, and a 92.4% increase since 2003. The number of total hip arthroplasty (THA) also increased by 12% from 2011 to 2012.[i] This is in keeping with a worldwide trend of increasing arthroplasty operations[ii], [iii]

Total joint arthroplasty surgery carries inherent risks. Anaemia due to blood loss remains one of the major complications from joint replacement surgery, and is relatively common. Bierbaum et al reported transfusion rates of 57% and 39% for total hip arthroplasty and total knee arthroplasty respectively[iv].

Across the globe orthopedic surgery is responsible for the highest percentage of allogenic transfusions compared with other surgical specialties. These procedures account for 9.8% of all red blood cell transfusions. Elective orthopaedic surgery utilised the most packed red blood cells compared to other surgical specialties. The only branch of medicine where there was greater demand for allogenic blood transfusion was haematology (33.6%) [v],[vi].

Osteoarthritis is the main cause of arthritis requiring TKA and THA[vii]. As osteoarthritis increases with age, so too does the relative co-morbidities of the patient.[viii] Surgical patients with greater co-morbidities are known to be at an increased risk of peri-operative morbidity and mortality[ix]. Thousands of patients undergo joint replacement as an elective procedure. Therefore it is extremely important to improve the safety of this operation and reduce the potential complications to ensure that patients achieve the desired improvement in their quality of life and the costs of care associated with these elective procedures are minimised.

This thesis will first evaluate the current evidence base for the current strategies employed by orthopaedic surgeons to achieve optimal blood transfusion management in total hip and knee arthroplasty. Following a review of the literature a series of prospective studies will be presented that aim to identify best practice in the operative management of allogenic blood transfusion for patients undergoing total joint arthroplasty.

INTRODUCTION

a) History of arthroplasty

Total hip arthroplasty has been identified as the gold standard to which other joints replacements have followed. It seems fitting to describe the history of the development of the total hip arthroplasty.

Joint arthropathy has been around for thousands of years [x]. Osteoarthritis is the most common aetiology of these arthropathies [xi].

In the pre anaesthetic era, amputation was the operation of choice for traumatic joint injuries suffered by causalities of war due to ease and speed of operation. Surgeons such as Henry Park (1744-1831) who worked at The Royal Infirmary advocated for joint excision creating an arthrodesis, 'thereby obtaining a cure by means of Callus'.[xii]

White, in 1821[xiii] and Barton, in 1826[xiv], both tried to manipulate the fusion of joints and halt the loss of movement by applying early motion to the excised area to create a pseudo-arthrosis. Those who survived the surgery however eventually went onto fusion at a later time.

A Frenchman named Léopold Ollier [xv] created worldwide interest in interpositional arthroplasty through the use of unfixed adipose tissue. Others tried different materials- both foreign and native. The first interpositional material to resemble today's implants was the use of an ivory ball and socket joint fixed to bone by nickel screws in 1891 by Themistocles Glück of Berlin.[xvi]

After failed attempts with other materials, Smith Peterson in 1937, with the help of a dental colleague, used Vitallium to produce good, reliable 10 year clinical results in moulded interpositional arthroplasty. [xvii]

Parallel with the aforementioned interpositional arthroplasty were further attempts at prosthetic hip arthroplasty. The Frenchman Delbet, (1861-1925) used rubber in 1919; Groves an Englishman tried ivory in 1927; and the Judet brothers trialled acryclic in 1948. All these attempts failed due to material wear. [xviii]

The classification of wear includes; adhesive wear, abrasive wear, third party wear, volumetric wear and linear wear. The common mechanism for each of these types of wear was the formation of debris. The foreign materials introduced into the hip joint lead to the recruitment of macrophages who through Rank ligand interactions induced osteoclastic activity and subsequent osteolysis or loss of bone stock. Prosthesis micromotion in turn increased wear and debris disseminated throughout the joint space further propagating osteolysis and consequent prosthesis failure .[xix]

Not all pioneers of joint arthroplasty followed the same direction. It is of interest to note that major developments in excisional arthroplasty still occurred throughout this time. In 1928 the eponymous Girdlestone procedure involving the resection of the femoral neck and head was popularised for treatment of infection and continues to be the fall-back option in failed arthroplasty revisions today.[xx]

Other noteworthy developments included the use of a metallic hemiarthroplasty by Moore and Bohlman in 1940 [xxi] and the use of acrylic bone cement for fixation by Haboush in 1952[xxii].

Focus must turn to the father of joint arthroplasty- Sir John Charnley. His significance to the field can be learnt from the manner in which he developed the answer to his original question.

'The cart has been put before the horse; the artificial joint has been made and used, and now we are trying to find out how and why it fails.' [xxiii]

After an already distinguished surgical career, Charnley in 1949, at age 38, set up a hip centre through which he sought to answer the aforementioned statement[xxiv]. The answer came through his low friction arthroplasty. By reducing the size of the femoral head to 22.2mm he reduced the torque transmitted from the head to the acetabulum. This is compared to Muller 30mm, Mckee-Farrar 41m and Weber 42mm designs. He believed any smaller would increase dislocation. [xxv] This counterintuitive solution was due to the fact that he speculated that a smaller femoral head size in the prosthesis would lead to reduced production of debris and subsequent osteolysis and thus, he hoped, would increase the longevity of his prosthesis compared to the others that were in contemporaneous use.

The next advancement by Charnley came through choice of material. He began by using polytetrafluoroethylene(PTFE) as the acetabular shell. Laboratory data differed from in vivo results. On review of the first 300 cases, PTFE induced a significant foreign body reaction, with increased wear rates.[xxvi] Charnley demonstrated the answer as to why this occurred, through experimenting on one's self, and in doing so explained the basis for osteolysis. Osteolysis is the loss of bone stock due to foreign body reaction to wear particles.[xxvii]

Ultra high molecular weight polyethylene was then inserted on the acetabular side in 1962 and has for decades now continued to be used because of its excellent wear properties[xxviii]

The third reason for Charnley's legacy came through the development of proper understanding of acrylic cement's role in total joint arthroplasty. While it had been used previously, Charnley understood its role not as glue but as a grout, leading to a tighter fit and greater area of implant to bone fixation.[xxix]

Charnley 's Low Fraction Arthroplasty resulted in a 0.21% revision rate (excluding infection and periprosthetic fracture) for loosening at 10 years compared with Muller's 10 % revision rate at ten years.[xxx]

Engineering advances in implant design have continued, aiming to reduce complications, such as peri prosthetic fractures and revision surgery. This has mainly occurred through the development of cementless prostheses and improvements of prosthetic materials, especially the bearing couples.[xxxi]

Total knee arthroplasty followed a similar pre implant surgical path to the hip, as previously mentioned, with excisional and interpositional arthroplasty. Following on from Charnley's success with total hip arthroplasty with polyethylene as a bearing surface and acrylic cement for fixation, total knee arthroplasty started to develop into a successful operation in the 1970s with the total condylar prosthesis. [xxxii]

Previously to this knee replacement suffered from high failure rates with the constrained hinged prosthesis[xxxiii]. Gluck used Ivory in 1891 to produce a hinge joint replacement.

In the 1970s total knee arthroplasty separated into two main philosophies; anatomical vs functional.

The anatomical approach revolved around preserving both cruciate ligaments to preserve femoral rollback and rotation, and was initiated by Gunston with the polycentric knee[xxxiv]. It was deemed too difficult for most surgeons to do well. It was also believed that the cruciate ligaments needed to be resected in order to correct the deformity. Further to this the complex nature of individual condylar anatomy was argued as too hard to surgically reproduce.

In contrast, the functional approach removed at least the anterior cruciate ligament and provided a single femoral condyle to roll in a single tibial trough. This allowed for increased contact area between the femur and tibia, which reduced point stresses and subsequent wear. The single femoral component also increased the area for cementation between the prosthesis and bone, to improve fixation (compared with separate medial and femoral condyles). An example of a functional TKA was first popularised with the Freeman – Swanson prosthesis.[xxxv]

The next differentiation in TKA design, which continues today, is posterior cruciate (ligament) retaining, versus posterior cruciate (ligament) substituting. Posterior Cruciate substituting was popularised by Insall. These designs are characterised by excision of the native posterior cruciate ligament and substitution with a post and CAM. [xxxvi]

Implant design advancement was followed by a greater understanding of the importance of surgical technique in outcome. Flexion and extension balancing was described by Freeman and expanded by Insall to improve patient range of motion and stability. [xxxvii] [xxxviii]

Over the years different techniques have been developed to improve implant alignment. These include intra-medullary vs extra-medullary jigs, computer assisted navigation, and patient specific instrumentation.

b) Transfusion History

While there are varying reports of blood transfusions throughout history, the first cannot be thought of as occurring before Harvey first described arterial and venous blood flow in 1628. There are reports of transfusion prior to this, however blood was mainly utilised via ingestion and medicinally. The basis for this usage was Hippocrates' theory of humors. Blood being one of the four humors considered necessary in the appropriate balance to prevent disease. Initial transfusions involved animal to humans.[xxxix] Transfusion had limited clinical scope due to transfusion reactions with ABO incompatibility unknown at the time.

Blood transfusion first became feasible and successful at the beginning of the 20th century. Landsteiner discovered ABO blood groups in 1901 to make blood transfusion biologically compatible. In 1907 Reuben Ottenberg performed the first blood transfusion using blood typing and cross-matching.[xl] Prior to this discovery, blood transfusions were associated with a 50% or greater mortality rate and were not considered safe medical practice.[xli] There were of often haemolytic reactions that were not understood. Initial blood transfusions were immediate from the donor to the recipient. The discovery that anticoagulation of blood donations could allow for collected blood to be refrigerated and stored meant that the donor did not have to be present for the transfusion to occur.

The advent of World War I meant that there was an exponential increase in the demand for the administration of rapid transfusions on the battlefield. Oswald Hope, a volunteer physician from USA, created the first known blood bank, changing practice from direct or

near same time transfusions, showed that a dextrose-citrate solution [xiii] would allow for the storage of blood for up to 26 days in glass vials.[xlii]

The need and use of transfusion continued into World War II. Blood transfusions during the world wars saved many lives and the risks of the procedure were not appreciated. The development of joint surgery and other elective surgery is becoming a more commonplace procedure in the period after world war two meant that the clinical indications for blood transfusions were quite liberal by today's standards.

In the civilian surgical setting Adams et al[xliii] proposed in 1942, the 10/30 rule as the standard transfusion trigger. This translated to a haemoglobin concentration of 10 g/dL and haematocrit level of 30% being the pre operative minimum and to transfuse any patient below this level regardless of symptoms. Adam's rationale was that anaemia affects the oxygen carrying capacity of blood and this subsequently would lead to insufficient oxygen to tissues. The scientific rationale to a haemoglobin of 10 g/dL was then suggested as the optimal haemoglobin concentration [xliv].

Adam's obstetric paper became the foundation for liberal transfusions being the main stay of practice. It wasn't until after this time that the hazards of transfusion became more apparent. Such problems as the risk of blood borne infections like hepatitis and then in the 1980s HIV. As a result of these and other non-infective risks associated with transfusion today the national blood authority of Australia sets a restrictive transfusion trigger; haemoglobin of 10g/dL as the maximum haemoglobin for patients suffering symptomatic anaemia, and 7g/dL as the objective value for transfusion[xlv] . The National Institutes of Health 1988 consensus conference report on red cell transfusion was one of the first to question this liberal transfusion strategy.[xlvi]

While hepatitis was a known adverse event from blood transfusion, it wasn't until 1963 that the 'red antigen' or 'Australian(au) antigen was discovered[xlvii]. This antigen is now recognised as the Hepatitis B surface antigen. In 1970 the National Institute of Health implemented a screening program for hepatitis B surface antigen, reducing hepatitis rates by 70%.[xlviii] Hepatitis C donor screening was introduced in the 1990s.[xlix] With the advent of screening systems, hepatitis incidence rates dropped from 30% pre 1970, to 10% in 1980s to a rate today that is estimated to be between 0.0001-0.0002 %[l]

1981 saw the first case report of what is now known as HIV[li]. The importance of adequate screening of donors for Hepatitis prevention became evident when it was realised that 90% of haemophiliacs had become infected with HIV prior to this initial case report.[lii] Screening tests now bring the incidence risk down to a similar rate as that of hepatitis, one per one to two million.

In addition to the transmission of infections from the donors to the recipients blood transfusions can cause harm to patients through causing sepsis caused by bacterial contamination. The storage of packed red blood cells in sterile glass containers and refrigerators largely reduced bacterial contamination.[liii] Bacterial sepsis due to a blood transfusion is approximately one in five hundred thousand incidence. This is largely due to skin flora.[liv]

Transfusion is now only part of today's blood management strategies. It is now important to review the evidence surrounding these other practices involved in blood management.

Literature search

The national blood authority of Australia has released guidelines with regard perioperative blood management in patients undergoing surgery.[lv] They carried out a systemic review of blood management strategies involved in surgery. It was my initial goal to review the guideline's suggestions and see how they relate to orthopaedic literature.

Liberal vs restricted transfusion.

As discussed in the introduction and history of transfusion, packed red blood cells were transfused to patients without hesitation in the post operative period to maintain a haematocrit of greater than 30, or haemoglobin of greater than 100g/L. Increasing concerns have been raised regarding the efficacy and safety of transfusion, as a result a more cautious, or restricted approach is now taken. The guidelines state 'patients should not receive a transfusion when the haemoglobin level is $\geqslant$100 g/L. In postoperative patients with acute myocardial or cerebrovascular ischaemia and a haemoglobin level of 70–100 g/L, transfusion of a single unit of RBC, followed by reassessment of clinical efficacy, is appropriate'. We now review the literature addressing the question of morbidity and mortality associated with transfusing with a liberal compared to a restricted transfusion trigger.

With regards to the orthopaedic literature there has been substantial literature considering when is the appropriate time to recommend a blood transfusion to a post operative patient. A small pilot study examined hip fracture patients and showed no difference in length of

stay, 30 or 60 day mortality in patients given packed red blood cells once their haemoglobin was less than 100g/dL (liberal) vs those given a transfusion when symptomatic with a haemoglobin of less than 100 g/dl (restrictive).[lvi]

Another study utilised the same transfusion trigger groups as above with a different hip fracture population. There were more cardiovascular events and greater mortality in the patients transfused when their haemoglobin was less than 100 (liberal) compared to the group transfused when symptomatic (restrictive), and no difference in functional scores or length of stay. These included arthroplasty patients as a treatment option for hip fracture.[lvii]

When we review patients from an exclusively elective arthroplasty population setting, it was shown that there was no difference in silent myocardial infarctions or days to discharge between liberal and restrictive transfusion groups during the post operative period.[lviii]

Effect of red blood cell transfusion on patient outcomes

*Mortality***-** In cardiac patients there has been shown to be an increased mortality rate in those who receive autologous transfusions [lix]. In non cardiac surgery patients, the answer is not as clear cut. The referenced study in the guidelines is a case controlled study of 229 hip fracture patients that showed an increased mortality in those who received transfusion of packed red blood cells after 90 days. [lx] A further literature search outside these guidelines revealed a study that demonstrated a similar finding, but on multivariable analysis the increased mortality is no longer true after accounting for other patient variables such as increased comorbidities(measured through ASA status) and age. [lxi] This multivariable result demonstrates the difficultly in inferring causality to mortality from transfusion due to confounders.

No direct arthroplasty studies have been identified that have demonstrated any impact on mortality by having a blood transfusion.

With time there has been shown to be increased morbidity directly related to transfusion. While the risks of reactions to the blood infused, along with contamination with viral or bacteria is well known, transfusion of blood has a systemic immune-modulatory effect on the body. If we now look at the morbidity related to transfusion in the post operative period. In an elective arthroplasty setting, it has been shown in a prospective study involving 444 patients that transfusion is associated with an increased risk of wound infection, and subsequently an increased length of hospital stay in patients undergoing total hip arthroplasty [lxii]. In a hemiarthroplasty group of 290 patients, transfusion appeared to be correlated with superficial wound infection, urinary infection and pneumonia. [lxiii]One of the studies utilized by the guidelines demonstrated that non cardiac surgical patients have adverse morbidity as the result of transfusion. 9.6% of the 6301 non-cardiac surgical patients were orthopaedic patients. Consider as part of this group, those receiving blood transfusion had a higher rate of pneumonia, however the orthopaedic subgroup was not evaluated on its own.[lxiv]

A further search of the literature outside the guidelines identified a cohort of 687 geriatric hip fracture patients and the only statistically significant complication associated with packed red cell transfusion was urinary tract infection. [lxv] The breakdown of surgical treatment- e.g. arthroplasty vs open reduction internal fixation, was not known.

An increased length of hospital stay is associated with a higher cost of admission. In addition to the elective hip arthroplasty setting above [lxvi], the guidelines also demonstrate there to be an increased readmission rate in hip fracture, however no patient was treated with a total hip arthroplasty and there was no difference in transfusion rates in those treated with hemiarthroplasty. [lxvii] Further literature review outside the guidelines revealed a retrospective study of 2,104 total hip arthroplasty patients that showed red blood cell

transfusion to be a risk factor for length of stay ***regardless*** of haemoglobin difference. This is **independent** of other factors such as age and warfarin/heparin(vs aspirin) which were shown to be other risk factors.[lxviii]

Pre operative anaemia

Having a lower haemoglobin level prior to surgery is known to be an independent predictor of morbidity and mortality in non cardiac surgery patients.[lxix] [lxx] Pre operative anaemia is also the biggest risk factor for allogenic transfusion in joint arthroplasty patients[lxxi], and with that comes the subsequent risk of adverse events associated with allogenic transfusion previously identified.

It therefore seems logical to improve preoperative haemoglobin levels. Methods to improve haemoglobin levels preoperatively include iron therapy and erythropoietin. Iron is needed in the synthesis of haemoglobin. Erythropoietin is a hormone naturally produced by the kidneys, which stimulates erythropoiesis/red blood cell production.

Iron and Erythropoietin- The guidelines suggest use of Iron therapy in patients with low ferritin and erythropoietin as well as iron in patients with anaemia of chronic disease.

A cohort study of 156 patients treatment with ferrous sulphate 256mg / day with combination vitamin C(enhances absorption) for 1 month preoperatively reduces transfusion rate for non anaemic patients in an orthopaedic population.[lxxii]

Erythropoietin has shown to be successful in improving; 1) mean preoperative haemoglobin and 2) post operative haemoglobin with reduced transfusion rates in the eight studies that it

was combined with Iron therapy in patients undergoing the following orthopaedic operations; hip fracture, hip and knee joint arthroplasty surgery.[lxxiii]

Effect of Perioperative cessation of medications

Patients presenting for joint replacement are often elderly. With this increasing age there is an increased number of comorbidities in these patients presenting for joint replacement[lxxiv]. Some medications to treat these co morbidities, such as warfarin, aspirin and clopidogrel, affectively reduce the effect of the clotting cascade. I will now review these medications and their effect on blood loss in surgery.

Warfarin is a medication which inhibits the extrinsic pathway of the clotting cascade used in the treatment of disease such as atrial fibrillation, venous thrombosis and heart valves which are associated with an increased risk of thrombotic disease[lxxv]. The guideline[lxxvi] recommends the cessation of warfarin for procedures with an estimated large volume blood loss but it can be continued for arthrocentesis, cataract surgery, upper gastrointestinal endoscopy or colonoscopy (with or without biopsy), as morbidity and mortality were unaffected when warfarin was continued. [lxxvii] Current recommendations suggest assessing individual thrombotic risk and adjusting perioperative bridging therapy based on it. CHEST physicians guidelines, where patients are risk stratified into high risk(>10% annual thromboembolic risk), medium(5-10% annual thromboembolic risk) or low risk(<5% annual thromboembolic risk). All groups cease their warfarin 5 days preoperatively. High risk patients are managed with bridging therapy where Enoxaparin is started to maintain therapeutic anticoagulation peri operatively where low risk patients are not. Warfarin is restarted 1-2 days post operatively once haemostasis is adequate.[lxxviii]

Data from outside the Australian blood Bank perioperative guidelines suggest bridging therapy has been shown to increase post-operative stay and cost of stay when the patient's warfarin is restarted.[lxxix] There have only been two other studies (Rhodes et al [lxxx]and Chana et al[lxxxi]) that have investigated the safety of continuing Warfarin in patients undergoing TKA.

Rhodes et al performed a retrospective study of 39 warfarinised patients undergoing TKA and found no increase in the rate of haemorrhage for patients on continuous warfarin. The second study by Chana et al was a case series of 24 patients on continuous warfarin undergoing TKA and reported no major haemorrhage and only one minor wound problem. Chana et al reported mean pre-operative INR of 2.2 and a mean change in INR of 0.4. Rhodes et al also reported mean pre-operative INR of 2.1 and a mean change in INR of 1.2.

Clopidogrel –is an antiplatelet medication commonly used in the prevention of recurrent transient ischemic attacks, strokes and coronary artery disease. It's safety in surgery is not certain from the guideline's recommendations as only one non cardiac study was identified that involved general surgical patients[lxxxii]. It was a small cohort study comparing those who received clopidogrel within 7 days of surgery vs greater than 7 days to surgery and there was no statistically significant difference found. Reviewing literature from outside the guidelines demonstrated two small series which showed no increase in blood loss or transfusion in hip fracture patients.[lxxxiii, lxxxiv]

Aspirin – is another antiplatelet medication used largely in the treatment of coronary artery disease. The guidelines recommend the cessation of aspirin prior to orthopaedic surgery if it does not pose a cardiovascular risk. This is on the premise that there was increased incidence of perioperative bleeding while on 100mg of aspirin, but the severity of the bleeds was not increased. Retrospective data shows a mean time between discontinuation of aspirin and complications as 8.5 days for acute coronary events and 14.3 days for cerebrovascular events. [lxxxv]

Utilisation of anti-fibrinolytics in Arthroplasty

The most common anti-fibrinolytic agent in use is tranexamic acid. It is a lysine analogue which competitively inhibits the conversion of plasminogen to plasmin. Plasmin breaks down fibrin. Fibrin is the final product in the clotting cascade, acting in unison with platelets to form the haemostatic thrombus. In the national guidelines discussing orthopaedic administration of tranexamic acid, it was only considered as IV administration and no dose recommendations were given within the national guidelines[lxxxvi]. There is no evidence for an increased incidence of myocardial infarction with unclear advice on the effect on thrombosis and stroke. This is based on a Cochrane review whose objective was to examine the evidence for the efficacy of aprotinin, tranexamic acid, and epsilon aminocaproic acid in reducing perioperative blood loss and allogeneic blood transfusion, and the evidence for any effect on clinical outcomes such as mortality and re-operation rates.[lxxxvii]

When examining the orthopaedic systematic review a dosing regimen of 10-15mg /kg IV was most common (max 1g) at induction. The relative risk for transfusion was 0.47 with a mean difference of 393ml in TKA and 639ml in THA vs placebo.

There was found to be no increased risk of thromboembolic disease, but few studies objectively looked for it, with only one study performing venous ultrasound on day 21. Given most of the DVT screening in the Cochrane orthopaedic review article occurred at day 3-5, if done at all and it cannot be safely assumed that there is no increased risk of venous thromboembolism, as it was screened for at too early a stage. The one study which did ultrasound on day 3 and 21 failed to show a difference in DVT incidence, but it only involved a study population of 40 patients. [lxxxviii]

A Further literature search demonstrated one study that has shown topical administration to be more effective when given at the same dose of 1.5g as intravenous in total knee arthroplasty. [lxxxix]

DVT prophylaxis

Continuing on the theme of thromboembolic disease post arthroplasty, although not included in the perioperative blood management guidelines, DVT prophylaxis is a contentious issue and deserves discussion. The natural history of DVT post arthroplasty is that the majority of DVTs begin and resolve within the first 3 days post operatively [xc] but 20% develop in previously thrombus free veins[xci]. 61% occur after day 3 with 9% occurring after the first week. [xcii]75% develop in the operated leg. [xciii] 75% of fatal post operative PEs occur between days 3-7 post operatively.[xciv] It would therefore have been optimal to evaluate objectively for DVT within the first 7 days post operatively of the tranexamic acid studies.

However, groups such as Kim et al, who showed a 20% and 41% incidence of DVT in Korean hip[xcv] and knee[xcvi] arthroplasty patients respectively, at day 7 without thromboprophylaxis, also demonstrated that without treatment there was a 100% resolution of DVTs in this patient group at 6 months with no objective evidence of pulmonary emboli, questioning the significance of DVT in this population. Care should be taken when applying these results to western patients due to genetic differences and associated co-morbidities seen in Western populations which may make the Korean studies falsely reassuring . Symptomatic DVTs present differently, with large population studies suggesting an incidence of between 1.2[xcvii] - 2.8%[xcviii], and they present much later in time. The mean presentation was shown to be at a mean of 7 to 16 days post operatively for total knee replacement, and, 17 to 27 days post operatively for total hip arthroplasty from large data studies from American [xcix] and

Scandinavian [c] populations respectively. This has resulted in longer duration thromboprophylaxis regimes to extend beyond the period of hospitalisation[ci].

While the goal of prophylaxis has been to decrease the incidence of DVTs and in so doing lead to a decrease in the subsequent incidence of pulmonary embolus and fatal pulmonary embolus; to date there has been no reduction in mortality able to be attributed to this intervention. [cii]**.** The all case mortality rate has been shown to be lower with the use of aspirin compared with low molecular weight heparin and warfarin, with no statistically significant difference in pulmonary embolus or fatal pulmonary embolus rates between chemical thromboprophylactic regimes[ciii]**.**

As a result the Australian Arthroplasty society now advocates for low dose aspirin as part of a multimodal thromboprophylactic regime in low risk patients(i.e. no previous thromboembolic disease). [civ]

The focus of this thesis is on perioperative blood transfusion management. Low Molecular weight heparin and warfarin(to a lesser extent) have a higher volume of blood loss and increase the risk of transfusion relative to aspirin.[cv]

With this increased blood loss there has been a higher incidence of wound complications, namely increased drain volume, superficial infection and deep infection requiring surgery in the warfarin group vs. aspirin.[cvi] Other studies have shown the method of thromboembolism prophylaxis has an effect on wound complications. Potent chemoprophylaxis has been associated with higher rates of wound drainage and other post-operative complications.[cvii] It has been demonstrated that there is a clear association between anticoagulants and periprosthetic joint infection after hip and knee replacement[cviii]. Patients treated with low molecular weight heparin vs aspirin had a longer time to a dry surgical wound. Each day of

prolonged wound drainage increased the risk of wound infection by 42% following a total hip arthroplasty and by 29% following a total knee arthroplasty[cix].

The time to initiate the chemical thromboprophylaxis is a balance between the prevention of thromboembolic disease and the risk of bleeding and subsequent morbidity risks. The optimal time therefore balances this risk, medications should be started with the target being the achievement of adequate anticoagulation at a circulation 8 hours post operatively. [cx]This allows for haemostasis of small vessels to be achieved during the operation and therefore reduced intra-operative blood loss. For example, in the case of low molecular heparin, it should be injected subcutaneously 4 hours post operation to reach effect at 8 hours, vs. 7 hours for unfractionated heparin.[cxi]

As indicated in the Australian Arthroplasty society guidelines[cxii] the potential morbidity associated with the increased risk of blood loss and wound complications needs to be balanced against the risk of DVT and pulmonary embolus on a patient-by-patient scenario.

Pre operative autologous donation

One idea that appears to have face validity is to have patients receive their own blood back during an operation after donating it pre-operatively. This method has gained favour because of the reported cases of transfusion acquired HIV and Hepatitis that occurred in the 1980s prior to the universal screening of blood donors. It was thought that by using one's own haemoglobin that you would be able to eliminate the risk of transmission of transfusion acquired infections and that there might be scope to be more liberal in its usage as it was the patient's own blood.

However, this approach did not lead to the hoped reduction in perioperative morbidity and indeed was found to lead to an increase in adverse outcomes. The donation of the blood

leads to a decrease in the pre operative haemoglobin in patients, which in turn, leads to an overall increased rate of transfusion, albeit autologous. Aside from the lack of clinical benefit autologous transfusion was found to be an expensive procedure. There is a high rate of wasted blood units with autologous donation, ranging from 40% to 56%, and therefore it is no longer deemed to be cost effective[cxiii]. Furthermore, the total cost of pre autologous donation is more expensive than allogenic transfusions [cxiv] and reported to be approximately 135% of homologous units due to logistical and tracking issues. Pre-operative autologous donation is also not free of risk with administrative error, the major cause of significant harm with the potential for the wrong blood being returned to the patient. [cxv]

Based on two Cochrane reviews[cxvi], [cxvii] which did not comment on any effect on mortality, morbidity or length of stay, the national blood authority perioperative guideline[cxviii] stated that Autologous transfusion is not recommended. The Australian Blood Bank consequently currently imposes a cost to patients if they wish to utilise pre-operative autologous donation.[cxix]

Operative factors

Depending on the surgeon, there are different variations in the approach in gaining access to the joint and completing the joint replacement. The choice of approach is often due to the training and experience of the surgeon.

Approach to the knee joint is largely the same, with most surgeons utilising a medial para-patellar approach as their arthrotomy.

The hip can be approached through anterior, lateral or posterior incisions, the posterior approach being the most common[cxx]. A systematic review comparing the anterior and posterior approach found a trend towards lower blood loss in the posterior approach but

this was not found to be statistically significant[cxxi], although individual studies suggest a 200ml total blood loss less in the posterior vs anterior approach[cxxii]. A comparison between lateral and anterior approaches found a significant difference between pre operative and day 1 post operative haemoglobin to be higher in the lateral approach(3.5 vs 3.1 g/dL)[cxxiii]

However, blood loss is not an absolute reason to choose an approach. Surgeon training often dictates which approach is utilised by a surgeon, and there is a significant learning curve when learning a new technique. This has correlated to increased operative times and increased blood loss is those learning the anterior hip approach.[cxxiv]

It has been shown that a *surgeon's experience level* effects the blood loss during surgery. Blood loss has been shown to be less in total hip arthroplasty for surgeons with a higher volume of cases and shorter operative time.[cxxv]

Blood in the surgical field can make visualisation difficult during surgery. Some surgeons use a *Tourniquet* to reduce blood flow of the area being operated on, commonly use in total knee arthroplasty. Others argue that by not using a tourniquet they are better able to identify larger blood vessels, ligate them and thus reduce the total overall blood loss (via decreased post operative blood loss). Nonetheless, the guidelines[cxxvi] advocate for the use of a tourniquet where possible. However in relation to total knee arthroplasty different meta analyses have concluded different views regarding intraoperative and total blood loss. Half of the recommendations state no difference in both intra and total blood loss where as the other half advocate that it has a protective effect.[cxxvii], [cxxviii], [cxxix] It would appear that there is no consensus with respect to the use or otherwise of the tourniquet .

Any joint replacement relies on fixation between the newly implanted prosthesis and the bone. There are *Cemented and Uncemented prostheses.* Cemented prostheses have been shown to result in a lower blood loss. [cxxx]There are pros and cons to any method of fixation and blood loss is not an absolute indication for choice of fixation.

Anaesthetic related

While not in direct control of the anaesthetist, *positioning* of the patient for a surgical procedure is done in a way to allow best exposure for the surgeon but still allowed the anaesthetist to monitor and intervene on the cardiorespiratory functions as needed. Lateral positioning in total hip arthroplasty has been shown to reduce blood loss as postulated by reduced venous engorgement due to the effect of, gravity.[cxxxi]

Anaesthetic is the process of rendering a patient 'without sensation' for a procedure. It involves using agents, which produce a combination of analgesia, lack of memory, unconsciousness and muscle relaxation, all to a varying degree depending on the patient and procedure to be performed. Different *Anaesthetic types* can effect blood loss. Spinal[cxxxii] and regional[cxxxiii] anaesthesia have both been shown to be effective at reducing blood loss in total hip arthroplasty but do not impact on blood loss that occurs during a knee replacement.

It is the anaesthetist's role to monitor and maintain the patient's cardiovascular and respiratory function throughout the anaesthetic period. *Intraoperative permissive hypotension*- supports the use of the lowest blood pressure that still maintains cerebral perfusion in an effort to decrease surgical blood loss. The guidelines suggest the use of intraoperative hypotension in patients who are not at an increased risk of cerebrovascular or cardiovascular events. Support for this approach is evidenced by a systematic review that demonstrated reduced blood loss and transfusion requirements with the use of intraoperative hypotension, with a mean 286ml less of estimated blood loss in the hypotensive(MAP mean 60mmHg) vs control(MAP mean 90mmHg) groups. [cxxxiv]

Anaesthetic agents are known to produce *hypothermia* to the unwarmed surgical patient. A Grade A recommendation is that there should be prevention of hypothermia during surgery

[cxxxv]. Hypothermia in anaesthesia is not clearly defined by the national blood authority guidelines and varies between studies. Some suggest maintaining the temperature greater than 35°C is adequate, whereas others suggest temperature should be maintained greater than 36°C.[cxxxvi]

This is contrary to normal thermoregulatory physiology, as normal body temperature averages 37°C and is rarely < 36.5°C [cxxxvii].Hypothermia during surgery is believed to be linked to adverse outcomes, such as an increased transfusion rate. There is no clear evidence that it has impacts on either the length of hospital stay or post operative haemoglobin. This recommendation is backed from data mainly relating to general [cxxxviii] and cardiothoracic surgery [cxxxix]. [cxl].

When looking at the orthopaedic literature, in particular arthroplasty, there is just one systematic review of three randomised control trials that have attempted to quantify the impact of changes in temperature in the theatre with the amount of intraoperative blood loss. The data from three studies on the effect of hypothermia and blood loss in total hip arthroplasty has produced inconsistent results. . 60(Schmied et al[cxli]), 50(Johansson et al[cxlii]), 150(Winkler et al[cxliii]) evaluated patients with temperature differences of 1.5, 0.8 and 0.5°C between comparator groups. Schmied et al and Winkler et al demonstrated a significant difference with 480 and 147 ml less mean total blood loss in the warmer group , Johansson et al found no significant difference between the two groups. Retrospective data has shown that active warming reduces transfusion requirements in total hip and knee replacements, but this study failed to demonstrate a change in haemoglobin levels with treatment [cxliv].

At this point in time there is very limited data that supports the fairly strongly expressed views surrounding the impact of maintaining a warmer temperature to reduce blood loss during total hip replacement and no study has specifically attempted to evaluate its role in total knee arthroplasty

Intra operative and post operative cell salvage

Cell salvage is a form of auto transfusion/ autologous transfusion, whereby red blood cells lost during or after the operation are collected and reinfused into the patient, in the hope of decreasing their overall volume and blood loss and subsequent risk of allogenic transfusion.

The guidelines state that it reduces transfusion requirements- both incidence and volume. The guidelines are uncertain as to if it reduces morbidity, mortality or length of stay.

Of the referenced articles one systemic review concluded that 96% of trials had poor methodology with poor randomisation. It also found cell salvage to be more effective in orthopaedic surgery than cardiac (RR 0.35 vs 0.82) in reducing autologous transfusion risk but no effect on length of stay and morbidity. Only one study involved over 200 patients, and two over 100 patients.[cxlv]

In a meta-analysis which focused more on orthopaedic surgery, washed and unwashed cell salvage devices were found to be effective at reducing allogenic transfusion risk with relative risk of 0.39 and 0.35 respectively. Cell salvage did not have any adverse events recorded, and the analysis did not comment on reducing mortality and length of stay.[cxlvi]

A further search of the literature identified a systematic review of anaemia and patient blood management in hip and knee surgery. This study found[cxlvii] that perioperative cell salvage decreased length of stay by 1 day[cxlviii] in total hip arthroplasty and 0.5 days in post operative cell salvage in total knee arthroplasty. [cxlix]

It is hard to give figures for cost effectiveness of cell salvage techniques. The total cost of allogenic blood needs to take into account direct and indirect costs. Direct costs include labour, equipment, infection tests, processing, inventory management, and compatibility tests in a mixed surgical population. Indirect: Discarded, crossover crossmatch, treatment of complications. Costs are normally presented as per unit of blood.[cl]

A unit of packed red cells in Australia costs $346.86.[cli]

No direct cost analysis exists for orthopaedic hip or knee arthroplasty surgery for cell salvage, and future cost analysis of it's efficacy is the recommendation of a review paper on cell salvage in arthroplasty . Cost analysis needs to take into account increased hospital costs with increased length of stay associated with allogenic transfusion. Equally, if cell salvage is used routinely, cost benefit calculations needs to consider that not all patients receive returned blood and certain patient cohorts are likely not to require any sort of blood salvage measure. Across surgical specialties the national blood authority in it's guidance for use of intraoperative cell salvage deemed it to be 'cost effective when used appropriately. Deciding when to use cell salvage in either routine or at risk patients is yet to be explored. A recent study has questioned the routine use of blood conservation strategies in primary TKA and THA when contemporary anaesthetic and surgical techniques and transfusion triggers are used.[clii]

Hypothesis/Aims

From the literature review, I wanted to contribute to a better understanding of orthopaedic arthroplasty and identify areas where there could be improvements in the understanding of what might be evidenced based best practice for managing intraoperative blood loss management. The search of the literature confirmed that there were two areas where there was an opportunity to study. The key questions I sought to answer through my research were:

1) Do changes in intraoperative body temperature during anaesthesia impact on the amount of blood loss and need for blood transfusion during total knee and hip arthroplasty?

2) What is the effectiveness of intraoperative Cell salvage during total knee and hip Arthroplasty? Does it's use accurately estimate the amount of blood loss during the procedures and does this result in a reduced need for blood transfusion either intra-operatively or post operatively?

Methods

Over the course of my enrolment I completed two research papers that are currently under peer review and have been accepted for publication. Each of the next two chapters are the result of my efforts to answer these two critical questions that arose from the my search of the literature:

Paper 1: *Blood loss in primary total knee arthroplasty—body temperature is not a significant risk factor—a prospective, consecutive, observational cohort study?*

The chapter that is presented is the manuscript that has been published in Journal of Orthopaedic Surgery and Research (2015).

Paper 2: *Analysis of the effectiveness of intraoperative cell salvage in primary total hip and knee arthroplasty*

The chapter that is presented is the manuscript that has been submitted to the Journal of Orthopaedic Surgery and is accepted for publication in 2016.

The methodology for each study is discussed in the methods section of both papers.

Both studies entail many methods that were common to both papers. In the appendix i) I outline the procedures that were common to both studies in greater detail than what has been described in the journal articles.

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Blood loss in primary total knee arthroplasty—body temperature is not a significant risk factor—a prospective, consecutive, observational cohort study

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Abstract

Background: Hypothermia related to anaesthesia and operating theatre environment is associated with increased blood loss in a number of surgical disciplines, including total hip arthroplasty. The influence of patient temperature on blood loss in total knee arthroplasty (TKA) has not been previously studied.

Methods: We recorded patient axillary temperature in the peri-operative period, up to 24 h post-operatively, and analysed the effect on transfusion rate and blood loss from a consecutive cohort of 101 patients undergoing primary TKA.

Results: No relationship between peri-operative patient temperature and blood loss was found within the recorded patient temperature range of 34.7–37.8 °C. Multivariable analysis found increasing age, surgical technique, type of anaesthesia and the use of anti-platelet and anticoagulant medications as significant factors affecting blood loss following TKA.

Conclusion: Patient temperature within a clinically observed range does not have a significant impact on blood loss in primary TKA patients. As long as patient temperature is maintained within a reasonable range during the intra-operative and post-operative periods, strategies other than rigid temperature control above 36.5 °C may be more effective in reducing blood loss following TKA.

Keywords: Hypothermia, Temperature, Knee, Arthroplasty, Blood management

Introduction

Blood loss during joint arthroplasty surgery can be significant and substantial, rendering the patient at risk of requiring an allogenic blood transfusion. Recent data has demonstrated arthroplasty and fracture surgery to account for 9.8 % of all transfused red blood cell units. It was the number one reason for transfusion in patients undergoing surgery, second only to haematology and oncology when considering all medical subspecialties [1]. Therefore, every effort should to be made to reduce the potential for blood loss and requiring allogenic blood during total knee arthroplasty (TKA).

Anaesthetic agents impair the control of body temperature and in combination with operating room temperature are largely responsible for the hypothermia associated with surgery. These agents result in loss of thermoregulatory controls through reduction of shivering and vasoconstriction [2–5]. Hypothermia results from an initial redistribution of heat from the core to the periphery, followed by ongoing decreased metabolic heat production and an increased cutaneous skin loss [6]. Surgical patients without active warming measures typically undergo a 1–2 °C fall in body temperature.

As a result, hypothermia during surgery theoretically produces increased blood loss. Hypothermia impairs the clotting cascade, resulting in increased prothrombin and

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activated partial thromboplastin times [7]. A decreased body temperature also decreases the production of thromboxane A2, which is responsible for platelet aggregation and activation, as well as vasoconstriction. The decrease in thromboxane A2 results in increased bleeding times [8, 9].

Whether hypothermia-induced coagulopathy results in clinically significant increased blood loss remains controversial. A meta-analysis of studies investigating hypothermia in different surgical specialties concluded that mild hypothermia does increase blood loss [10]. Three studies have looked at the effect of hypothermia and blood loss in total hip arthroplasty, with varied conclusions. Schmied et al. [11] and Winkler et al. [12] demonstrated significantly less blood loss in the warmer patient group, with as little as 0.5–1.5 °C temperature difference. In contrast, Johansson et al. [13] found no significant difference between the two groups with an average 0.8 °C variation in temperature. A retrospective study showed active warming reduces transfusion requirements in total hip and knee replacements, but this study failed to demonstrate a change in haemoglobin levels with treatment [14]. Despite conflicting results in the literature, NHMRC guidelines recommend the use of hypothermia prevention strategies to reduce the incidence of transfusion and blood loss during surgery.

In order to clarify the impact of patient temperature on blood loss in TKA, we undertook this study. Our aim was to determine if peri-operative body temperature affects blood loss during TKA. The study hypothesis is strict maintenance of patient temperature above 36.5 °C will lead to a significant reduction in blood loss in patients undergoing primary TKA.

Methods

The study is a prospective, consecutive, observational cohort of 101 patients undergoing primary TKA between January and June 2013 by two surgeons in the same orthopaedic department. Revision and bilateral procedures were excluded from the study. Ethics approval was obtained through the Hospital's Regional Ethics Committee, and all patients gave informed consent prior to inclusion in the study.

A medial parapatellar approach without tourniquet was used in all patients. One surgeon (surgeon B) used computer navigation for alignment and preparation, with cementation of all components in 55 patients. The other surgeon (surgeon A) employed intramedullary instrumentation, with a hybrid prosthesis for the remaining 46 patients. The patella was resurfaced in all patients. All knees were closed in layers with an intra-articular drain, which was removed in day 1 post-operatively. All patients commenced immediate weight bearing and active range of motion from day 1 post-operatively.

Both surgeons used mechanical devices for deep vein thrombosis (DVT) prophylaxis, together with either rivaroxaban 10 mg daily initiated 6 h post operation (surgeon A) or enoxaparin 40 mg daily initiated 4 h post operation (surgeon B). Patients already on coumadin pre-operatively or with a history of previous pulmonary emboli continued their coumadin peri-operatively, aiming for a target international normalized ratio (INR) of 2 on the day of surgery. In addition, aspirin (100 mg) was used in patients deemed high risk for cerebrovascular or cardiovascular complications. The patients on clopidogrel converted to aspirin 100 mg daily, after ceasing clopidogrel 5 days pre-operatively.

Patient axillary temperature was recorded at specific time points during the peri-operative period, including pre-operatively in the anaesthetic bay, post-operatively prior to leaving the operating theatre, prior to exiting the recovery room and then at six hourly intervals for the first 24 h post-operatively. The patients were divided into three temperature groups; less than 36 °C, between 36 and 36.5 °C and greater than 36.5 °C.

Blood loss was measured using three methods: (1) intra-operative blood loss, calculated as the difference between total suction volume and known irrigation volume; (2) post-operative blood loss using drain volume; and (3) total blood loss using the difference between pre-operative and day 1 post-operative haemoglobin levels.

Data on other factors believed to affect blood loss was also collected. These included age, sex, body mass index, heart rate, blood pressure, type of anaesthesia, operation time and the use of anticoagulant and anti-platelet medications [15, 16]. The number of units of allogenic blood transfused for each patient was recorded. The transfusion trigger was haemoglobin of less than 70 g/L or less than 100 g/L in patients with symptomatic anaemia or significant comorbidities [17].

Prior to study commencement, a power calculation was performed. To achieve 80 % power with 5 % significance level, 21 patients were required in each temperature group to detect a clinically significant difference of 8 g/L of haemoglobin between the low and normal temperature groups. Given the study was observational, estimation from previous studies on temperature and blood loss in THA required at least 100 enrolled patients to achieve 21 patients in the low temperature group. Results were described using proportions, means and standard deviations. Simple and multivariable linear regression was used to determine predictors of each of the three measures of blood loss. Interaction terms were fitted between significant predictors of the outcomes and the temperature group variable.

Results

The patient demographics are summarized in Table 1. There is no statistically significant difference between the surgeons in mean age of their patients (68.1 versus 68.5). Surgeon A had 60.1 % male patients, whereas B had 49.9 % male patients.

The mean operating theatre temperature was 19.6 °C. The average operative time was 81 min (SD 33 min). The mean pre-operative haemoglobin was 143 g/L (SD 14). The mean estimated intra-operative blood loss was 128 mL (SD 266). The average post-operative drain volume was 255 mL (SD 213), with an average haemoglobin difference from pre-operative to day 1 post-operative of 27.2 g/L (SD 10.5). There was no significant correlation between each of the three outcome measures of blood loss, as shown in Fig. 1.

Pre-operatively, patient temperature ranged from 34.3 to 37.2 °C, and post-operatively from 34.7 to 37.8 °C. The minimum temperature recorded at any time point was 34.3 °C. Only two patients recorded temperatures below 35 °C in the pre- and post-operative periods. The mean patient body temperature at each time point was similar: pre-operative 36.1 °C (SD 0.5), operative 36.1 °C (SD 0.6) and post-operative 36.3 °C (SD 0.4). We therefore used immediate post-operative temperature to assess the effect of body temperature on blood loss. The patient body temperature was not found to be associated with increased blood loss for any of the three measurement outcomes of blood loss. The results of patient temperature on blood loss are summarized in Table 2, separating each blood loss parameter and temperature group according to surgeon. Although the surgeon was a significant predictor of blood loss outcomes, the interaction with temperature category was not significant. Therefore, overall results were used to assess the relationship between temperature and outcomes.

Table 1 Patient demographics, pre- and post-operative findings

Characteristic	Statistic
Total number of patients	101
Gender	
Male	55 (56.5 %)
Female	46 (45.5 %)
Age mean (SD)	68.6 (9.2)
BMI mean (SD)	30.6 (4.8)
Surgical technique	
Surgeon A intramedullary	46 (45.5 %)
Surgeon B computer navigation	55 (56.5 %)
Heart rate mean (SD)	68 (12)
Systolic blood pressure mean (SD)	131 (23)
Anaesthetic	
General	7 (6.9 %)
Spinal	2 (2.0 %)
Regional	3 (3.0 %)
General and regional	38 (37.6 %)
General and spinal	1 (1.0 %)
Spinal and regional	37 (36.6 %)
General spinal and regional	13 (12.9 %)
Operative time mean (SD)	81 min (33)
Anticoagulant/antiplatelet medications	
Rivaroxaban	40 %
Low-molecular-weight Heparin	38 %
Aspirin	8 %
Warfarin	5 %
Other	9 %

Both univariable and multivariable analyses were used to evaluate factors influencing blood loss in our cohort of TKA patients. The results are outlined in Tables 3 and 4, respectively.

Using intra-operative volume loss as outcome, predictors of blood loss are increased age and surgical technique. Surgeon B who used computer navigation had on average 131 mL less blood loss than surgeon A. Each year of increased age resulted in 10 mL greater blood loss. Higher pre-operative systolic blood pressure and female gender appeared to increase blood loss but were not statistically significant.

Significant univariable predictors of higher drain volume included surgeon, operative time, type of anaesthesia and type of anticoagulant medication. Using multivariable regression analysis, patients undergoing TKA under general combined with regional anaesthesia, spinal plus regional, or general plus spinal plus regional had significantly less drain volume blood loss compared to general anaesthesia alone. The use of low molecular weight heparin, coumadin, aspirin, or combination of aspirin and low-molecular-weight heparin resulted in significantly less blood loss than the use of rivaroxaban. The use of aspirin in addition to rivaroxaban caused increased blood drainage loss when compared with rivaroxaban alone.

The two variables predictive of total haemoglobin loss are surgeon and requirement for allogenic blood transfusion. Surgeon B had on average 4.9 g/L less haemoglobin loss than surgeon A. The patients who received an allogenic blood transfusion had on average 9.3 g/L more haemoglobin loss.

Discussion

The results of our study failed to demonstrate any effect of patient temperature during the peri-operative period, within the range we observed between 34.3 to 37.2 °C, on blood loss in primary TKA. Measuring blood loss through intra-operative suction volume, post-operative

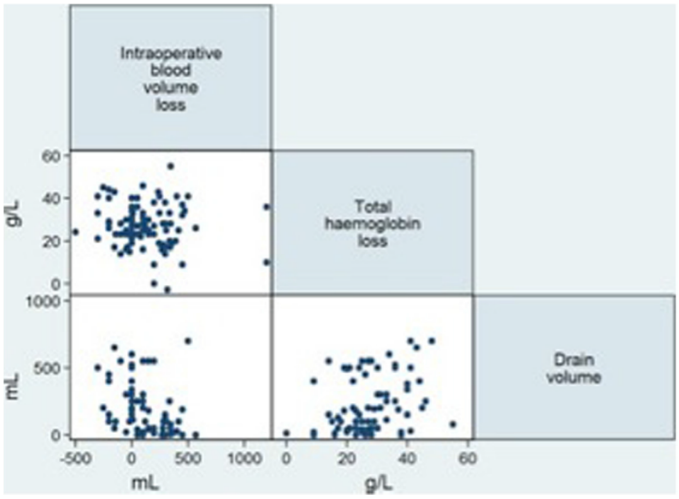

Fig. 1 Scatterplot matrix of the three measures of blood loss

drainage and post-operative change in haemoglobin, no difference could be demonstrated in patients with temperatures below 36 °C compared to patients with a normal temperature above 36.5 °C. This resulted in no difference in allogenic transfusion rate between the patient temperature groups. Therefore, our hypothesis that maintaining patient temperature at 36.5 °C and above during TKA will result in reduced blood loss was not substantiated.

Our study is not suggesting that anaesthesia-induced hypothermia is inconsequential or that patient temperature monitoring is unimportant. Maintenance of patient temperature may have a greater role in countries where ambient temperatures are usually low. Hypothermia may also have a significant role in other complications such as infection following TKA. What we are suggesting is that within the clinically observed temperature range, using routine patient warming techniques, blood loss was not affected. Therefore, rigid maintenance of patient temperature above 36.5 °C through further active warming techniques may not be necessary in reducing blood loss in TKA.

Our study design does have a number of weaknesses and limitations. The study did not include a control group. We did not feel it would be ethical to intentionally expose patients to a low temperature situation, given what is known from other fields of surgery and current best practice guidelines [17]. We aimed not to determine the effect of active warming, but rather look for a correlation between lower body temperature and blood loss in the primary TKA, which we believe our observational prospective study allowed us to do. Secondly, the patient cohort was derived from two surgeons with differing surgical technique. However, the

Table 2 Intra-operative and post-operative blood loss by temperature category immediately post-operatively

Outcome		Low temperature group (<36.0 °C) $n = 26$	Low normal temperature group (36.0 °C–36.5 °C) $n = 51$	Normal temperature group (>36.5 °C) $n = 24$	p values*
Mean blood volume loss mL (SD)	Surgeon A	218 (184)	155 (269)	137 (199)	0.77, 0.93
	Surgeon B	130 (179)	90 (324)	125 (456)	
	Overall	140 (205)	101 (300)	133 (302)	
Mean haemoglobin loss g/L (SD)	Surgeon A	22.2 (11.8)	26.7 (11.1)	24.1 (6.8)	0.39, 0.53
	Surgeon B	31.1 (10.9)	30.9 (10.0)	25.0 (9.7)	
	Overall	26.4 (12.0)	28.7 (10.7)	24.5 (7.7)	
Mean drain volume mL (SD)	Surgeon A	51 (69)	75 (77)	90 (73)	0.70, 0.48
	Surgeon B	389 (189)	348 (196)	493 (105)	
	Overall	213 (220)	235 (208)	260 (213)	

Surgeon A used intramedullary instrumentation, surgeon B used computer navigation

*p values are for the comparison between (a) low temperature and normal temperature groups and (b) low normal temperature and normal temperature groups

Table 3 Univariable analysis of predictors of blood loss following total knee arthroplasty

	Intra-operative blood loss (mL)		Post-operative drain volume (mL)		Change in haemoglobin (g/L)	
Predictors	Regression coefficient (95 % CI)	*p* value	Regression coefficient (95 % CI)	*p* value	Regression coefficient (95 % CI)	*p* value
Age	10.4 (2.3–18.6)	0.01	−3.4 (−8.9 to 2.0)	0.22	0.14 (−0.08 to 0.37)	0.21
Female gender	140.5 (−12 to 293)	0.07	93.6 (−2.1 to 189.3)	0.06	−0.001 (−4.3 to 4.3)	0.99
BMI	3.1 (−13.5 to 19.8)	0.7	9.1 (−1.0 to 19.1)	0.08	−0.38 (−0.83 to 0.07)	0.09
Surgeon	220.3 (71.6 to 369.1)	0.004	317 (253 to 382)	<0.001	−4.90 (−9.08 to −0.72)	0.02
Heart rate	1.35 (−5.3 to 7.95)	0.7	3.9 (−0.7 to 8.5)	0.10	0.02 (−0.17 to 0.22)	0.81
Systolic BP	3.3 (−0.06 to 6.7)	0.054	−1.0 (−3.8 to 1.7)	0.46	0.06 (−0.03 to 0.16)	0.18
Anaesthetic type (reference category is general anaesthetic alone)						
Spinal	−108.57 (−952 to 734.9)	0.80	−393 (−829 to 44)	0.08	−23 (−62 to 16)	0.24
Regional	45 (−921.28– 1011.28)	0.93	154 (−144 to 452)	0.31	−18 (−15 to 52)	0.46
General + regional	−250 (−1161.02 to 661.02)	0.59	−162 (−369 to 46)	0.13	−14 (−34 to 6)	0.17
Spinal + regional	−210 (−0.46 to 568.10)	0.57	−210 (−417 to −4)	0.05	−16 (−36 to 4)	0.12
General + spinal + regional	−166.11 (−965.67 to 633.45)	0.68	−361 (−622 to −99)	0.01	−25 (−47 to −2)	0.03
Operative time	1.19 (−1.36 to 3.74)	0.36	−5.3 (−7.3 to −3.2)	<0.001	0.02 (−0.06 −0.11)	0.61
Medication (reference category is rivaroxaban alone)	NA					
Low-molecular-weight heparin			−312 (−387 to −237)	<0.001	−11 (−22 to 16)	0.06
Warfarin			−205 (−378 to −32.6)	0.02	−10 (−33 to 14)	0.41
Aspirin			−332 (−505 to −159)	<0.001	−6 (−13 to 25)	0.56
Aspirin + Rivaroxaban			97 (−40 to 235)	0.16	17 (−7 to 39)	0.16
Aspirin + LMWH			−287 (−414 to −160)	<0.001	−1 (−22 to 20)	0.92

primary aim of the study was to determine if patient temperature had an effect on blood loss. Both surgeons used the same operating theatres with identical surgical environment. The use of multivariable analysis was able to separate the effects of surgeon technique from other factors to ensure that the study conclusions remain valid. Thirdly, the three cohorts of patient temperature varied by only 0.5–1 °C. Whilst the effect difference is small, we believe this reflects real clinical practice and makes the findings applicable to what surgeons would routinely observe. In addition, previous studies have reported even mild hypothermia ($<1^0$ C) significantly increases surgical blood loss by approximately 16 % and the relative risk of transfusion by 22 % [10]. Fourthly, our method for determining intra-operative blood loss may not be the most accurate and reliable approach. We observed a large standard deviation for intra-operative blood loss of 389 mL from a mean of 70 mL and included some patients with a negative difference. The method used does not account for blood on the drapes or blood taken up by surgical sponges. To overcome this weakness, blood loss was also estimated using two other methods including post-operative drain volume and change in haemoglobin. None of the three measures for blood loss in our study were affected by patient temperature, so we feel our conclusions are still valid. Finally, pulmonary artery temperature is considered the gold standard for temperature measurement. Our study used axillary temperature as the best non-invasive method and the most practical technique for daily clinical practice. Axillary temperature has been shown to compare well with pulmonary artery temperature [18] and is equivalent to other invasive measures of core temperature such as intravesical and rectal temperature [19]. Whilst ideally core temperature would have been a more accurate method of measurement, we used a consistent reproducible technique for axillary temperature across the whole patient cohort and therefore feel our methodology is still justifiable and credible. As we recorded temperatures up to 24 h post-operatively, including in the recovery room and surgical ward, using invasive methods was not possible. Our aim was to determine the effect of patient temperature on blood loss even after departure from the operating room.

In our results, there was no correlation between intra-operative blood loss, post-operative drain volume and

Table 4 Multivariable analysis of predictors of blood loss following total knee arthroplasty

Intra-operative blood loss (mL)		
Predictor	Regression coefficient (95 % CI)	*p* value
Age	10.3 (4.8 to 15.9)	<0.001
Surgeon B	−131 (−235 to −27)	0.01
Drain Volume (mL)		
Predictor	Regression coefficient (95 % CI)	*p* value
Medication (reference category is rivaroxaban alone)		<0.001
Low molecular weight heparin	−282 (−360 to −205)	<0.001
Warfarin	−238 (−406 to −70)	0.01
Aspirin	−300 (−464 to −137)	<0.001
Aspirin + rivaroxaban	133 (−2 to 267)	0.05
Aspirin + LMWH	−232 (−372 to −93)	0.001
Type of anaesthetic (reference category is general anaesthetic alone)		0.02
Spinal	−290 (−621 to 41)	0.09
Regional	24 (−187 to 236)	0.82
General + regional	−193 (−341 to −45)	0.01
Spinal + regional	−201 (−350 to −51)	0.01
General + spinal + regional	−218 (−410 to −26)	0.03
Haemoglobin loss (g/L)		
Predictor	Regression coefficient (95 % CI)	*p* value
Surgeon B	−4.3 (−8.5 to −0.1)	0.04

change in haemoglobin. Hidden blood loss from tissue extravasation, residual knee blood volume and haemolysis commonly observed following TKA is most likely to account for this observed variation [20].

Several other factors were highlighted to affect blood loss during primary TKA in our study. In common with previous literature, our results demonstrated age, surgical technique, anaesthetic type and type of anticoagulant medication used for DVT prophylaxis to impact blood loss. The exact cause of the age effect is not clear and cannot be determined from the data collected in our study. We postulate older patients have higher blood pressures, combined with reduced arterial tone and capillary fragility, causing greater intra-operative blood loss. Although age is a non-modifiable risk factor, it is important to appreciate its impact and to optimize pre-operative haemoglobin more diligently in elderly patients prior to surgery.

There was also a significant difference in blood loss between the two surgeons. A hybrid prosthesis was used by surgeon A and fully cemented prostheses by surgeon B. However blood loss has not been found to be associated with prosthesis type in terms of fixation in TKA [21]. We believe the difference in blood loss relates to instrumentation and type of anticoagulant, with both factors contributing significantly. Surgeon A used intramedullary instrumentation whereas surgeon B used computer-assisted navigation. Computer navigation has previously been demonstrated to produce reduced blood loss [22, 23], as a consequence of avoidance of violating the femoral and tibial intramedullary canals.

Our study reinforces the concept of regional and spinal anaesthesia having a protective effect against blood loss and is the first from our review to show a protective effect in TKA. Regional anaesthesia results in decreased arterial blood pressure [24], whilst spinal anaesthesia leads to venous hypotension and a decreased venous pressure at the surgical site [25].

Rivaroxaban was shown to be associated with a significantly higher drain volume than low-molecular-weight heparin, aspirin and coumadin. Aspirin in combination with rivaroxaban increased drain volume over rivaroxaban alone and resulted in the greatest blood loss. Our study results contrast previous reports showing no significant difference between low-molecular-weight heparin and rivaroxaban and may reflect the surgeon effect on thrombophylactic preference not accounted for by multivariable analysis [26]. The patients continuing coumadin in the peri-operative period with an INR of 2 on the day of surgery was associated with a lower drain volume than patients treated with low-molecular-weight

heparin and rivaroxaban. The practice of continuing coumadin without cessation in patients already taking the medication pre-operatively or in patients with previous history of pulmonary emboli was utilized by both surgeons and supports a growing trend that peri-operative bridging therapy and coumadin cessation may not be necessary or the most effective strategy in patients undergoing TKA [27].

Conclusions

Peri-operative patient temperature, within the clinically observed range from 34.3 to 37.2 °C, did not affect blood loss or the need for allogenic blood transfusion in patients undergoing TKA in our study. Avoiding hypothermia is an important aspect on peri-operative patient care; however, rigid temperature control above 36.50 °C may not be necessary to reduce blood loss in primary TKA and other factors may be more important including anticoagulant and anti-platelet medications use, the use of computer navigation and type of anaesthesia. Routine patient warming techniques that maintain patient temperatures within a reasonable range are sufficient to prevent clinically significant hypothermia-induced blood loss following TKA.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MD is the lead author responsible for the study design, data collection, analysis and interpretation and critically appraised the manuscript for submission. He has given approval of the final version to be published and is accountable for all aspects of work at the highest standard. SM and PJ are the authors responsible for the data collection and critically appraised the manuscript for submission. EB is the statistician involved in the data collection, analysis and interpretation and critically appraised the manuscript for submission. DL is the senior author. He and RR are the operating surgeons responsible for the study design, analysis and interpretation and critically appraised the manuscript for submission. They have given approval of the final version to be published and are accountable for all aspects of work at the highest standard. All authors read and approved the final manuscript.

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Title

Intra-operative Red Cell Salvage in Primary Total Hip and Knee Arthroplasty

Intra-operative Red Cell Salvage in Primary Total Hip and Knee Arthroplasty

Abstract

Purpose

The aim of our study was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary hip and knee arthroplasty.

Methods

The study comprises a retrospective analysis of 371 consecutive patients undergoing primary hip or knee arthroplasty with concomitant use of intra-operative cell salvage. The percentage of patients requiring allogenic transfusion despite cell salvage was the primary outcome. Other factors affecting transfusion risk were analysed.

Results

The overall transfusion rate was 16%. 24% of hips and 12% of knees received allogenic blood. Despite routinely utilising cell salvage in all cases, only 59% of hips and 63% of knees received returned red cells. Significantly greater blood loss occurred in the patients who were given returned red cells. Transfused patients had a significantly lower pre-operative haemaglobin, less intra-operative blood loss and were less likely to receive cell salvage blood. Pre-operative haemoglobin less than 120 g/L, female gender, and age greater than 75 was associated with a higher risk of allogenic transfusion. Patients receiving allogeneic transfusion had a longer hospital stay and greater complication rate.

Conclusions

Intra-operative cell salvage reduces but does not eliminate the need for allogeneic blood transfusion in primary hip and knee arthroplasty. The efficacy of cell salvage is related to haematocrit and volume of the blood lost. Intra-operative cell salvage on its own is not effective in patients with a

pre-operative haemaglobin less than 120g/L and should be combined with additional strategies such as correcting pre-operative anaemia.

Keywords: Cell salvage, arthroplasty, blood management, transfusion.

Introduction

Total hip and knee arthroplasty may result in substantial peri-operative blood loss, leading to post-operative anemia and rendering the patient at risk of requiring an allogenic blood transfusion. Bierbaum et al reported transfusion rates of 57% and 39% for total hip arthroplasty (THA) and total knee arthroplasty (TKA) respectively [1]. Total joint arthroplasty and fracture surgery is responsible for the highest percentage of allogenic transfusions compared with other surgical specialties [2,3].

Allogenic blood however is associated with risks to the patient, including disease transmission, hemolytic reactions, immunomodulation, hemodynamic overload, acute lung injury, and coagulopathy [4]. Previous studies have demonstrated an increased risk of postoperative infection, length of hospital stay and mortality in patients who receive allogenic blood [5,6,7]. Consequently, various blood conservation strategies have been employed in THA and TKA to reduce the need for allogenic blood.

Pre-operative autologous donation does reduce allogenic blood requirement [8,9,10,11], however is associated with a high rate of unused blood and is not cost effective [12,13,14]. The effectiveness of acute normovolaemic haemodilution in reducing transfusion need is debatable [15]. Studies on the use of post-operative reinfusion drains report a risk reduction in allogeneic transfusion [16,17,18].

Reinfusion drains however carry the potential for transfusion reactions as unwashed blood contains fibrin degradation products and other potential contaminants [19,20].

The intra-operative cell salvage technique used at our hospital incorporates washing of blood collected during surgery prior to reinfusion. We favor this method of blood conservation as it causes minimal disruption to surgical workflow and removes biochemical, cellular and non-cellular debri such as activated clotting factors, fatty lipids, and bone [21,22]. We have routinely used intra-operative cell saver with washed red cells in THA and TKA, in

the belief it would eliminate allogenic blood transfusion requirement and improve patient outcomes.

The primary aim of our study was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary THA and TKA, by determining the percentage of patients requiring allogenic transfusion and comparing this with traditional transfusion rates reported in the literature [1]. The secondary aim was to identify risk factors predicting the requirement for allogenic transfusion in patients who underwent cell salvage and establish how to optimize the effectiveness of cell salvage. Whilst previous studies have already reported on the benefits of cell salvage in THA and TKA [23,24,25,26,27,28], our study cohort is an updated review reflecting contemporary techniques in arthroplasty surgery including anaesthesia, surgical technique and individualization of transfusion trigger.

Materials and Methods

The study comprises a retrospective analysis of 371 consecutive patients undergoing primary THA and TKA with concomitant use of intra-operative cell salvage from January 2010 to December 2011. From the currently available literature, similar studies have reported the proportion of patients requiring transfusion to be approximately 20%. Therefore, in order to obtain a 95% confidence interval, we calculated 246 patients would be required for sufficient power for the study. Ethics approval was obtained from the Hospitals Regional Ethics Committee.

One surgeon performed all surgeries, using the same prosthesis, surgical technique and identical post-operative protocol in all patients. The hips were performed through an antero-lateral approach with the patient in the lateral position. Uncemented acetabular and femoral components were inserted in all patients, without use of a drain. The knees were performed through a standard medial para-patellar approach without tourniquet. Computer

navigation was utilized for alignment and preparation, and cemented femoral, tibial and patella components were used in all patients. An intra-articular drain on low suction was removed day 1 post operatively for the knees. All patients received enoxaparin 40mg daily for venous thromboembolic prophylaxis, commencing 4 hours post-operatively and continued for 14 days for TKA and 28 days for THA. Aspirin was continued through the peri-operative period if the patient was already on the medication prior to surgery.

Intraoperative cell salvage was performed in each case with the Haemonetics Cell Saver 5+ machine (Braintree, MA, USA). The salvaged blood was washed and concentrated prior to reinfusion. Reinfusion was commenced in the recovery room and completed on return to the ward. Hemoglobin levels were checked day 1 post-operatively. Transfusion trigger was patient specific, based on recommendations by the National Blood Authority of Australia. Haemoglobin of less 80g/L was an absolute trigger and less than 100g/L with symptomatic anemia and significant co-morbidities a relative indication for transfusion [29]. The relative indication for transfusion was based on the surgeon's best judgment according to the patient's symptoms and risk of complication such as myocardial events.

Our primary objective was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary hip and knee arthroplasty, by determining the percentage of patients requiring allogenic transfusion despite cell salvage. Additional data collection included demographics, complications, days until discharge, and hemoglobin change from pre-operatively to day 1 post-operative. Blood loss was measured and calculated using three methods of cell salvage volume, post-operative drain volume in TKA patients, and the difference between pre-operative and post-operative hemoglobin.

Results were described using proportions for binary variables, means and standard deviations for normally distributed variables and medians and inter-quartile ranges for

variables not normally distributed. We analysed using simple and multivariable logistic regression to determine predictors of need for transfusion.

Results

Demographics of the study cohort are summarized in table 1., including the proportion of patients in each category of pre-operative hemoglobin level. Eight percent of patients started with pre-operative hemoglobin less than 120g/dL, with the rate being 3 times higher in THA patients.

The overall transfusion rate was 16%, with 24% of THA patients and 12% of TKA patients requiring allogenic blood despite intra-operative cell salvage. Our results demonstrate a statistically significant decrease in allogenic transfusion rates compared to the historical non-cell salvage population of Bierbaum. A summary of transfusion rate of the current study compared with previously published literature is presented in tables 2 and 3 for THA and TKA respectively.

Blood loss outcomes for the 371 patients are shown in table 4. A pertinent finding is only 63% of knees and 59% of hips actually received returned red cells. Comparison of patients who received returned red cells with those who didn't is displayed in table 5. Significantly greater intra-operative blood loss occurred in the cell salvage group, with a mean of 362.48mls compared to 156.15mls. Intra-operative blood loss ranged from 200mls to 1200mls in the salvage group, in contrast to 50mls to 350mls in the non-salvage patients. Only 9 patients, in whom salvaged blood could not be obtained, had intra-operative blood loss greater than 200mls. From our data, a minimum of 200mls intra-operative blood loss is required to have sufficient volume to cell salvage.

Table 6 compares patients who received allogenic blood transfusion versus patients who did not. Significantly, transfusion risk was reduced with greater intra-operative blood volume loss, higher pre-operative haemaglobin and if the patient received salvaged blood. Our philosophy was to use an individualized variable transfusion trigger. Mean post-operative haemoglobin in the transfused patients was 103.46g/L compared to 121.65g/L in the non-transfused patients. The difference was statistically significant. The post-operative

haemaglobin in patients who required allogenic blood ranged from 71g/L to 110g/L. Allogenic transfusion requirement significantly increased length of hospital stay and incidence of peri-operative complications.

Using multivariable regression analysis, female gender, pre-operative haemaglobin less than 120 g/L, and age greater than 75 years proved to be significant risk factors for requiring allogenic blood, despite the use of intra-operative red cell salvage. Results of the univariable and multivariable analyses are shown in table 7. Four patients in the study group had a BMI less than 20. All 4 of these patients required allogenic transfusion, however the numbers were too small to allow statistical analysis.

Discussion

An effective blood management strategy is one of a number of critical components required for the successful care of joint arthroplasty patients. Significant blood loss may occur following THA and TKA, resulting in post-operative anemia, hindering patient recovery or leading to the need for allogenic blood transfusion. Allogenic transfusion has been shown to be detrimental to patient outcome and recovery following joint arthroplasty surgery [30,31,32].

Intra-operative red cell salvage re-infuses fresh blood and avoids problems with storage of red blood cells seen with autologous pre-donation and allogeneic red blood cells. This translates to more efficacious oxygen carrying red blood cells with a higher mean erythrocyte viability [33] and increased preservation of 2-3 diphosphoglycerate [34]. The technique also incorporates washing the blood loss volume, thereby removing contaminants and concentrating the reinfusion volume.

Our study has shown intra-operative cell salvage does significantly reduce transfusion requirements in primary THA and TKA compared to traditional rates reported in the literature. However we observed a substantial number of patients still required allogenic blood despite the use of red cell salvage. Patients undergoing THA were more likely to require allogenic blood. This appears to be a consequence of an increased proportion of THA patients with pre-operative hemoglobin less than 120g/L and potential for greater hidden blood loss into the thigh and buttock following THA.

One noteworthy finding of our study is only about 60% of patients actually received returned red cells. Nearly half the patients did not receive back any of their own blood lost during surgery. It appears for cell salvage to be effective, a critical amount of blood loss is necessary. Processing returned red cells is an interaction of volume loss and haematocrit of the blood salvaged. From our data, average blood loss in the patients receiving returned red cells was 362mls, range 200mls to 1200mls, compared to average 156mls, range 50mls to 350mls in the group with insufficient loss to salvage. A minimum of 200mls intra-operative blood loss is required to cell salvage, dependent also on the haemaglobin of the blood lost. Paradoxically, anemic patients require greater blood loss intra-operatively to be able to utilize cell salvage effectively. This further emphasizes the importance of correcting pre-operative hemoglobin, in our results to a minimum of 120g/L.

Reflecting the above observations, in our cell salvage cohort a greater intra-operative blood loss and higher pre-operative haemaglobin resulted in a significantly reduced risk of allogenic transfusion. Patients who received returned red cell were less likely to require allogenic blood, confirming its protective effect. In keeping with previous literature, receiving allogeneic blood was detrimental to our patients' recovery, culminating in a longer hospital stay and higher incidence of complications.

We demonstrated patients with low hemoglobin pre-operatively were at higher risk of requiring allogenic blood despite the use of cell salvage, emphasizing the need to identify and correct pre-operative anemia prior to surgery [15,35]. In our cohort, the critical

haemaglobin level was 120g/L, which increased the transfusion risk by 30 times compared to patients with haemaglobin above 150g/L. There were several non-modifiable factors, such as age and gender, which increased transfusion risk, highlighting the need to be diligent and proactive in these patient groups in correcting or optimizing other factors.

Our study does have several limitations and weaknesses. Being a retrospective study predisposes the data to recall and selection bias. We did not have a control or comparison group. Instead we chose to compare our results with transfusion rates reported in the literature. We cannot therefore be sure our results are purely due to the use of cell salvage technique alone and not other factors. Care should be taken when comparing our study with other cell salvage studies, which may have different patient populations, cell salvage devices, transfusion triggers, anesthetic practices and surgical technique. We did not use a tourniquet when performing TKA, which increases intra-operative blood loss. However increasing intra-operative blood loss during TKA should increase the benefits of intra-operative cell salvage. We also concede the use of intra-articular drains has now been shown to increase transfusion risk and a drain in TKA is often no longer routinely used. Recent studies have focused on hemostatic agents such as tranexamic acid, showing excellent effectiveness in reducing blood requirements following both THA and TKA [36,37,38]. Our study cohort did not receive any form of tranexamic acid, which has now become common practice in joint arthroplasty. Additionally, our patients continued aspirin during the peri-operative period in the belief this would be cardio-protective. However a recent large randomized controlled trial of 10010 patients of which 39% underwent orthopaedic procedures, comparing aspirin versus placebo with 30 days follow up after surgery, found contradictory results [39]. There was no difference in the primary outcome of death or myocardial infarction between the 2 groups, regardless of whether the patient was taking aspirin prior to surgery or not. Aspirin increased the risk of major bleeding compared with placebo. The authors concluded aspirin administration before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding. We no longer routinely continue aspirin unless absolutely necessary.

Nevertheless, we believe our study retains relevance as cell salvage remains one of a number of options available in a blood management strategy and is still commonly used. It is relatively simple to implement into the surgical algorithm and can be combined with other modalities. Our study was a consecutive series with sufficient numbers to be able to deduce several important conclusions.

Avoiding allogenic blood following THA and TKA has taken on increased significance due to the escalating cost of blood banking and stored blood. Therefore, intra-operative cell salvage should be incorporated in a comprehensive blood management strategy. Whilst cell salvage is effective in reducing allogenic blood requirements, other strategies should be used in combination, including maximizing pre-operative hemoglobin, using appropriate antifibrinolytic agents such as tranexamic acid and individualizing the transfusion trigger. The ultimate aim is allogenic blood requirement in elective THA and TKA should be zero.

Conclusion

Intra-operative cell salvage reduces but does not eliminate the need for allogenic blood transfusion following primary THA and TKA. A critical amount of intra-operative blood volume loss of 200mls and pre-operative hemoglobin above 120g/L is required for cell salvage to be effective. Future studies are required to define the ideal and most cost effective blood management program in THA and TKA.

Tables

Characteristic	THA (n=135)	TKA (n=236)	Total (n=371)
Female gender	86 (63%)	130 (55%)	216 (58%)
Age > 75	39 (29%)	62 (26%)	101 (27%)
Age years (mean, range)	70 (17- 91)	70 (47 – 95)	70 (17 – 95)
BMI kg/m^2 (mean, range)	27.4 (15.7 – 43.8)	30.3 (18.5 – 52.2)	29.2 (15.7 – 52.2)
BMI category			
<20	3 (2%)	1 (<1%)	4 (1%)
20 – 25	47 (35%)	30 (13%)	77 (21%)
>25 – 30	45 (33%)	98 (42%)	143 (39%)
>30	40 (30%)	107 (45%)	147 (40%)
Diagnosis			
Osteoarthritis	119 (88%)	230 (97%)	349 (94%)
Inflammatory	2 (1%)	4 (2%)	6 (2%)
Other	14 (10%)	2 (1%)	16 (4%)
Pre-op Hb g/L (mean, range)	134 (72 – 170)	138 (103 – 177)	137 (72 – 177)
Pre-op Hb category			
>= 150g/L	20 (15%)	63 (27%)	83 (22%)
>=120 – 150 g/L	95 (70%)	162 (69%)	257 (69%)
<120 g/L	20 (15%)	11 (5%)	31 (8%)

Table 1. Demographics of the study population.

Study	Bierbaum [1]	del Trujilo [24]	Smith [25]	Moonen [26]	Our Data
Allogenic Transfusion Rate	57%	15%	8%	6%	23.7%

Table 2. Effects on Allogenic Transfusion Rates of autologous re-transfusion of salvaged blood cells in randomized controlled trials and cohort studies for THA compared to historical rate reported by Bierbaum without intervention.

Study	Bierbaum [1]	Shenolikar [27]	Thomas [28]	Munoz [40]	Our Data
Allogenic Transfusion Rate	39%	16%	7%	11%	11.9%

Table 3. Effects on Allogenic Transfusion Rates of autologous re-transfusion of salvaged blood cells in randomized controlled trials and cohort studies for TKA compared to historical rate reported by Bierbaum without intervention.

Outcome	THA (n=135)	TKA (n=236)	Total (n=371)
Transfused	32 (24%)	29 (12%)	61 (16%)
Whole blood loss mL (mean, range)	271 (50 – 1200)	290 (100 – 950)	283 (50 – 1200)
Red cells returned	79 (59%)	149 (63%)	228 (61%)
Volume cell salvaged (mL)‡	205 (40 – 890)	193 (10 – 650)	197 (10 – 890)
Hb loss to day 0* g/L (mean, range)	17.7 (-34 – 40)	18.7 (-12 – 47)	18.3 (-34 – 47)
Hb loss to day 1** g/L (mean, range)	27.3 (-29 – 53)	29.1 (6 – 56)	28.4 (-29 – 56)
Knee drain volume mL (mean, range)	---	209 (0 – 800)	---
Any surgical complication	29 (21%)	45 (19%)	74 (20%)
Days to discharge (mean, range)	6 (3 – 16)	6 (3 – 30)	6 (3 – 30)

* Pre op Hb minus day 0 post op Hb

** Pre op Hb minus day 1 post op Hb

‡ In those with cell salvage only (n = 228)

Table 4. Transfusion, blood loss and outcomes for THA, TKA and combined cohort of patients.

Characteristic	**Cell Salvage Status**		**Mean Difference (95% CI)**	**p-value**
Outcome	**Yes**	**No**		
Pre-operative Hb [g/L; mean (SD)]	137.40 (14.03)	135.85 (12.76)	1.6 (-1.4- 4.5)	0.30
Blood Loss [mL; mean (SD)]	362.48 (136.69)	156.15 (52.06)	206.3 (182.8- 229.8)	<0.001

Table 5. Comparison of pre-operative haemaglobin and intra-operative blood volume loss according to patient cell salvage status.

Outcome	Transfused (n=61)	Not Transfused (n=310)	Total (n=371)	Difference (95% CI)[§]	p-value[§]
Pre-operative Hb. [g/L; mean (SD)]	122.76 (14.26)	139.61 (11.54)	136.80 (13.56)	-16.9 (-13.5- -20.2)	<0.001
Whole blood loss [mL; mean (SD)]	245 (156)	290 (148)	283 (150)	-45.6 (-4.4- -86.8)	0.03
Red cells returned [count (%)]	29 (48%)	199 (64%)	228 (61%)	-16% (-3%- -30%)	0.02
Volume cell salvaged [mL; median (IQR)]	156 (130 - 270)	150 (135 - 250)	150 (135 – 250)	6 (N/A)	0.40
Hb loss to day 0* [g/L; mean (SD)]	19.3 (13.2)	18.1 (8.2)	18.3 (9.3)	1.2 ()	0.38
Hb loss to day 1** [g/L; mean (SD)]	28.4 (16.2)	28.5 (8.4)	28.4 (10.1)	-0.1 (-3.0- 2.8)	0.95
Post-op Hb Day 1 [g/L; mean (SD)]	103.46 (11.04)	121.65 (12.60)	118.46 (14.14)		
Knee drain volume [mL; mean (SD)***]	205 (162)	210 (170)	209 (169)	-4.8 (-73.4 - 63.7)	0.89
Time to discharge [days; median (IQR)]	6 (5 - 8)	5 (5 - 7)	5 (5 - 7)	1 (N/A)	0.01
Any surgical complication [count (%)]	29 (48%)	45 (15%)	74 (20%)	33% (20% – 46%)	<0.001

§ 95% confidence intervals and p-values are for the difference between transfused and not transfused groups

*** in 27 transfused patients and 197 non-transfused patients with knee surgery

Table 6. Comparison of blood loss and outcomes for patients who received allogenic blood transfusion and patients who were not transfused.

Univariable analysis			
Risk factor	**Odds ratio**	**95% C.I.**	**P-Value**
Female gender	3.5	1.8 – 6.8	<0.001
Age >75	5.2	2.9 – 9.2	<0.001

Procedure - hip*	2.3	1.3 – 4.0	0.004
Diagnosis inflammatory**	1.2	0.1 – 10.1	0.75
Diagnosis other**	4.62	1.74 – 12.28	0.002
Hb <120 g/L***	44.4	12.8 – 154.3	<0.001
Hb >=120 <150 g/L***	2.5	0.8 – 7.3	0.21
BMI < 20 ****	NA	NA	NA
BMI >25 – 30 ****	0.34	0.17 – 0.67	0.002
BMI >30 ****	0.23	0.11 – 0.48	<0.001
Multivariable analysis			
Risk factor	**Odds ratio**	**95% C.I.**	**P-Value**
Female gender	2.8	1.2 – 6.6	0.02
Age >75	5.9	2.9 – 12.1	<0.001
Hb <120***	30.1	7.5 – 121.6	<0.001
Hb >120 <150 g/L***	1.3	0.4 – 4.1	0.32

* Compared with knee replacement

** Compared with diagnosis = osteoarthritis

*** Compared with Hb >150g/L group.

**** Compared to 'normal' BMI category of 20 – 25

Table 7. Univariable and multivariable analysis of risk factors for allogenic blood transfusion with the use of intra-operative red cell salvage.

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Discussion

The aim of this thesis is to identify what are the optimal methods for reducing blood loss in total joint surgery, specifically knee and hip arthroplasty.

Through review of the current best practice guidelines for blood management in surgery by the National Blood Authority of Australia I was able to identify areas considered best practice lacking evidence with regard to total joint arthroplasty. These included;

1) Avoiding hypothermia in surgery. There was no evidence for this in knee replacement surgery. My first paper addressed this.
2) Cell Salvage. Currently available studies in arthroplasty involve small numbers and it was unclear which population of patients benefited from it's use as according to the national blood authority guidelines. My second paper addressed these issues

Each paper individually describes and discusses the strengths and weaknesses of each paper's findings separately. This discussion therefore aims to expand, and not repeat the individual discussion of each paper.

Relation to other research

1) Blood loss in primary total knee arthroplasty—body temperature is not a significant risk factor—a prospective, consecutive, observational cohort study?

This is the first paper to look at temperature and its association with blood loss in total knee arthroplasty. Our paper demonstrated that temperature variations do not have a significant

association with blood loss in total knee arthroplasty. Our study differs from hip arthroplasty where previous studies have reported even mild hypothermia (<1^0 C) significantly increases surgical blood loss by approximately 16% and the relative risk of transfusion by 22%[cliii]. As a result of our study, resources should be spent on other areas to prevent blood loss in TKA. Other factors were shown to be significant for blood loss: age, surgical technique, anaesthetic type and type of anticoagulant medication used for DVT prophylaxis.

Computer navigation has previously been demonstrated to produce reduced blood loss[cliv,clv]], as a consequence of the femoral and tibial intramedullary canals not being violated. Another major difference in surgical technique was the use of hybrid prostheses by surgeon A (femoral component uncemented) and fully cemented prostheses by surgeon B. Blood loss has not been found to be associated with prosthesis type in terms of cement vs cementless fixation in TKA previously, and given the variables in our paper, we are not in a position to answer this question [clvi].

Already demonstrated in hip arthroplasty[clvii] this is the first study to show a protective effect of regional and spinal anaesthesia in total knee arthroplasty against transfusion. Regional anaesthesia results in decreased arterial blood pressure [clviii], whilst spinal anaesthesia leads to venous hypotension and a decreased venous pressure at the surgical site [clix].

Regarding bleeding and choice of thromboprophylaxis our results differ with that from larger clinical trials of rivaroxaban and enoxaparin, given we found higher bleeding with rivaroxaban than with enoxaparin[clx]. Patients continuing warfarin with an INR of 2 on the day of surgery was associated with a lower drain volume than patients treated with low molecular weight heparin and rivaroxaban. The practice of continuing coumadin without cessation in patients already taking the medication pre-operatively or in patients with previous history of pulmonary emboli was utilised by both surgeons and supports a growing trend that peri-operative bridging therapy and coumadin cessation may not be necessary or the most effective strategy in patients undergoing TKA [clxi]. See appendix ii) further

information on a study I was involved in. Again while I was an author, it is not my original work and therefore is not included within the thesis.

2) Analysis of the effectiveness of perioperative cell salvage in primary total hip and knee arthroplasty

There are a number of randomised control trials for cell salvage techniques. Our aim was to show a reduced transfusion rate in our population. This has been proven previously in three randomised control trials. Our other aim was to analyse this population of patients (arthroplasty) and better define who received benefit from the use of the cell saver(i.e. did not need transfusion).

We found hip patients were more likely to require allogeneic blood mostly likely due to the greater potential for hip patients to have hidden blood loss in the post-operative period into the thigh and buttock. Patients with low hemoglobin pre-operatively were also at higher risk, emphasizing the need to identify and correct pre-operative anaemia prior to surgery. Whilst we also identified non-modifiable factors such as age, gender and hips, and this highlights the need to be more diligent in these patient groups in correcting or optimizing other factors. These findings are consistent with Bierbaum's historical paper[clxii].

We were also able to demonstrate the adverse consequences of being transfused. Those transfused in our study had a statistically significantly longer hospital stay and higher incidence of post-operative complications. Allogeneic transfusion has been shown to be detrimental to patient outcome and recovery following joint replacement surgery. In an elective arthroplasty setting, it has been shown in a prospective study involving 444 patients that transfusion is associated with an increased risk of wound infection, and subsequently an increased length of hospital stay in patients undergoing total hip arthroplasty[clxiii]. In a hemi-arthroplasty group of 290 patients transfusion appeared to be correlated with superficial wound infection, urinary infection and pneumonia[clxiv]. Another retrospective

study of 2,104 total hip arthroplasty patients showed red blood cell transfusion to be an independent risk factor for length of stay regardless of hemoglobin difference[clxv].

Significantly where our study expanded the literature was understanding and identifying patients with a pre-operative haemoglobin of 120-150 as likely to benefit most from cell salvage. The amount of blood loss required for the red cell salvage process and be returned as blood to the patient is a complex interaction between volume loss and the hematocrit of the blood lost. Paradoxically, anaemic patients pre-operatively have to lose more blood intra-operatively to be able to cell salvage. If the haematocrit is low this will mean that it requires a greater volume of salvaged blood to produce a given number of packed cells for re-infusion into the patient. This means if the patient commences the operation with a low hemoglobin they will have to lose even more blood to have enough red cells to be able to returned the patients than those with a high hemoglobin and it becomes ever more likely that they will then need a blood transfusion. Patients with a haemoglobin of >150 are unlikely to require cell salvage to prevent allogeneic transfusion. Those with a preoperative haemoglobin of <120 should undergo measures to increase preoperative baseline haemoglobin. This will not only decrease their risk of transfusion, but also improve the effectiveness of cell saver in this population by allowing a higher haematocrit of reinfused cell salvage red blood cells.

Challenges

A key area of learning from conducting this research was the recognition of the fallibility of our methods for estimating intra-operative blood loss. These methods should have been best reviewed in greater detail prior to conducting the research in the methods section of the thesis. However it was only after conducting the research that inaccuracies in our measurements became apparent. The challenges that we experienced in this research when the literature was interrogated in more detail are not unique and perhaps represent the challenge that is implicit in trying to make the operating theatre a precise research laboratory.

Blood loss measurement

--- *Intraoperative blood loss measurements*

Given the wide range of values (including negative values), our methods for determining intraoperative blood loss was deemed inaccurate.

A number of methods for calculating intra-operative blood loss exist, including; visual estimation, direct measurement, weight, photometry and other miscellaneous methods

- Quick and non-labour intensive; *visual estimates* has been shown to be a poor representation of actual blood loss [clxvi] and when used in clinical practice, visual estimation often leads to poor transfusion practices[clxvii]

Direct measurement best describes our method of collection. Collecting blood into a container, in our case the suction container. It, however, is contaminated by other fluid sucked up such as synovial fluid, irrigation fluid, and misses blood absorbed by gauzes and swabs, on drapes and spilt onto the floor. Without some estimation or measurement of these losses, this method may be inaccurate.

Weighing blood by collecting all contaminated surgical drapes, linen, towels, or gauze and then deducting the dry weight of the items. This method requires an accurate scale and is labour intensive. It also does not discriminate between other fluids contributing to the contaminated weight, such as irrigation fluid. This method has been proven to be an accurate method.[clxviii]

Photometry involves dissolving blood from absorbent theatre material to alkaline haematin with measurement of the optical density to determine intraoperative blood loss, which has been shown to have accuracy within 10% of actual blood loss[clxix]. It is far more labour

intensive and expensive given the equipment and qualified individuals required to utilise this method.

Notable miscellaneous techniques include ultrasound measurement of superior vena cava volume and radiographic red cell labelling. These are not practical currently.

---*Calculating total blood loss*

We used haemoglobin for total blood loss given it is our clinical reference in everyday practice as doctors/surgeons. However, using haemoglobin as measure for blood loss assumes a constant total blood volume, and is therefore only an estimation of true blood loss. Several formulas have been developed to calculate total blood loss.

Blood volume (PBV) can be calculated using the formula of Nadler, Hidalgo and Bloch[clxx]:

PBV = kl x height (m)3 + k2 x weight (kg) + k3

where kl = 0.3669, k2 = 0.03219, k3 = 0.6041 for men;

kl = 0.3561, k2 = 0.03308, k3 = 0.1833 for women

Multiplying the haemocrit against the blood volume will give the total red cell volume. As such ;

Brooke first described blood loss as a logarithmic function.[clxxi]

$$\text{Estimated blood loss} = BV \times (\ln Hct_0 \ \ln Hct_t)$$

Hct0= preoperative value and t= final haemocrit post operatively

'Gross formula' uses average haematocrit to reflect the linear change that is isovolumetric haemodilution (as blood volume falls, fluid shift to maintain intravascular volume), and how average haematocrit reflects this[clxxii]

$$\text{Estimated blood loss} = \text{EBV} \times \frac{\text{Hct}_0 - \text{Hct}_f}{\text{Hct}_{AV}}$$

Gross validated his formulae in arthroplasty surgery.

Meunier calculated a formula involving haemoglobin based off blood donors. However, it was concluded that haemoglobin underestimates blood loss due to time taken for haemodilution. [clxxiii]

--- *Calculating post operative blood loss*

In both our studies we used post operative drain volume to reflect post operative blood loss. This ignores residual blood in the joint, hidden blood loss into the surrounding soft tissues, and fails to account for blood loss due to haemolysis. As such Sehat et al developed a formula to more accurately calculate hidden blood loss.

The hidden loss can then be determined by subtracting the visible loss from the calculated true total loss, then adding the volume re-infused or transfused. The results were converted to whole blood volume for each patient, again using their average haematocrit. [clxxiv]

---*Reflection of other blood loss measurement methods and if should they have been utilised in our studies*

The paper on cell saver focused on analysing cell saver in preventing transfusion and identifying risk factors for transfusion in a arthroplasty population, based on separating the population into transfused vs non transfused cohort. Intraoperative blood loss was accurately calculated utilising cell saver volume. Quantifying blood loss using other methods would not have affected the cell saver reinfused volume and therefore would not have added greater utility to our study. Haemoglobin is the utilised clinical transfusion trigger along with patient evaluation.

In contrast the study analysing temperature and blood loss in knee arthroplasty focused on blood loss and not transfusion. Therefore more accurate measures to quantify the three areas of blood loss should have been utilized. Our intraoperative method should have accounted for blood loss to other areas (e.g. gauze), our total blood loss would have been more accurate with the Gross formula and our post operative blood loss should have taken into account hidden blood loss.

Temperature

Temperature is not a constant variable. It naturally changes with time, during a day with circadian rhythm, varies from day to day, for example with ovulation in females. It also changes based off metabolic state, activity levels, and as we age we are unable to produce extremes of temperature. The external environment also causes changes in temperature via the external temperature and our external clothing as a response. While normal temperature is stated as having a normal range of 36.5- 37.5 °C, it has been shown to have a much wider variation in a review of the literature.[clxxv]

What is a normal temperature also varies on the method used to measure it. Pulmonary wedge catheter measurements are the gold standard for measuring temperature. Rectal, vesical, vaginal are more invasive ways of measuring temperature. Tympanic, oral and axillary are less invasive. Axillary and oral temperatures typically measure a lower temperature than the other methods which are estimates of core body temperature.[clxxvi]

Theatre temperature was recorded to see if it had an effect on body temperature, however, we were unable to show this. All other external factors contributing to patient temperature were difficult to record, e.g. blankets, warmed fluids as mentioned in the section difficulties of the *operating theatre as a laboratory*.

As acknowledged in our study, it was extremely difficult to account for variations in temperature and external factors contributing to it. However, given it was an observational study, we did our best to monitor for changes by measuring at different time points and using the most reproducible non invasive temperature assessment- axillary temperature. Our results therefore accurately reflect real clinical practice.

Data collection

The Cell saver paper was the largest analysis of an arthroplasty cohort utilising the cell saver. The Data was reviewed retrospectively. Data collection and entry was exhaustive and labour intensive. For each subject of the cell saver paper it required 45-60 minutes to complete, as the recorded admission information was incomplete and other databases, such as the pathology results database, had to be interrogated to find missing data. Furthermore, local General Practitioners were contacted as an additional resource for finding missing data.

Given the data was retrospective and a large volume to review, selection and recall bias clouds our results, mainly for the post operative complications. This means that although

one would think that retrospective data collection might be easier, my own experience from these two studies was that I suspect the retrospective data was actually more challenging and the final information was less robust because of it.

Comparing this to prospective data collection used in the temperature study, my chart review time was minimal. A form was designed and placed on the patients chart from time of admission to discharge to allow for the necessary data to be recorded by the surgical fellow of Dr Liu and Randle at the time. However when reviewing the data for statistical analysis it was clear that not all forms were filled out correctly, at times with missing and incorrect data. The data form was often completed by nursing staff, when the fellow was not available. Selective retrospective review of admission charts was needed to find missing data and adjust some input at times. We suffered from attrition and change in methods bias that is typical of prospective studies. Training of research assistants would have improved the quality of the information collected.

Human based research

Experimenting on humans brought limitations to our study. Given the patients were from a private hospital there was a further expectation not to intervene in these patients. A side aim of this research might be the effort required to also evaluate one's own clinical work would hopefully lead to an improvement in the quality of what was being done. I think this misconception that research is something best left to the public sector is misconceived-and our study is evidence of benefit to practice by evaluation of this private sector group of patients.

However studies had to be designed in line with current treatment practice the same as a patient that was not in the study would receive.

While temperature and blood loss had never been explored in knee arthroplasty, other areas of surgery had showed a detrimental effect with increased blood loss in hypothermic patients. Given best practice guidelines advised against hypothermia it could not be justified to actively lower a knee replacement patient's temperature to separate the two arms of the experiment. This only allowed us to do an observation study. We therefore required more patients in the study as the majority of temperatures lay within the middle range in between the low temperature group and normothermic group.

In the cell saver population, there wasn't a direct comparison group from the same surgeon and as a result historical literature had to be referred to as the comparator, which has inherent statistical problems by comparing different populations.

It also meant extra efforts had to be made with storage and entry of data to protect patient confidentiality.

On a plus side observing current treatment and with differing outcomes meant our results were directly applicable to and able to give great insight into current clinical practice!

Operating theatre as a laboratory

Few practices in surgery are evidenced based instead they are largely historical. General surgery has 50% the evidence based practice compared with internal medicine[clxxvii]. This is complicated by the rapid development of surgical treatments confounded by the historical post anaesthetic discovery period and the commercial interests guiding decision making processes and development[clxxviii].

New techniques are subject to the surgeon's learning curve, practice effect reflecting higher complications when a new procedure is undertaken by a surgeon compared with a stable,

previously used technique. Given Dr Liu and the local hospital preference was to use cell saver in all patients, this made the study a historical control study, which can overestimate the benefits of an intervention due to other advances in the field over time. [clxxix]

The challenges of trials in surgery have previously been documented. They largely relate to the difficulties in comparing treatment options in surgery, due to innate surgical ability and decision making varying between surgeons and patient selection for operation (along with different patient groups) differing, making randomisation difficult [clxxx].

This was evident in our first study on temperature and blood loss in total knee arthroplasty whereby the individual surgeon was found to be a large influence on blood loss. While all variables were recorded and compared with multivariable analysis, this has no doubt reduced the ability of the study to examine specifically the effect of body temperature on blood loss due to confounders.

Differing patient populations have different characteristics. We tried to best account for this through multivariable analysis of demographic and physiological characteristics.

Patients had different comorbidities, often on different medications (specifically aspirin, clopidogrel and warfarin), and receiving different anaesthetic if one form was contraindicated because of a comorbidity or antiplatelet medication. Again these were accounted for with multivariable analysis.

Surgeons had different practice variations- as explored in the temperature study we found a difference in blood loss between surgeons. Again we tried to account for these by multivariable analysis including the surgeon and thromboprophylactic medications.

The cell saver paper was a single surgeon paper and removed the influence of differing practice to the results.

The more humans involved in a study leads to an increased chance of human error with results. Issues with data collection as discussed above reflect this.

Overall while an imperfect laboratory, we sort clinical answers from a real time clinical environment. The clinical setting is not a controlled experimental laboratory setting, but is based on variable doctor, patient and environmental factors. Multivariable analysis helped us reduce confounding variables influencing results, while still gaining clinically relevant results.

Future directions/implementation strategy

By submitting the articles to peer reviewed journals and presenting the studies at national and state orthopaedic meetings it was hoped the evidence is delivered to orthopaedic arthroplasty surgeons in an appropriate manner to allow them to change practice as accordingly seen fit.

The results generated from the masters project will help develop best practice guidelines more specific to arthroplasty surgery than the current national blood authority of Australia's guidelines. Dr David Liu, my clinical supervisor, was invited to write a review article on the topic of blood management in arthroplasty surgery.

While the results from my studies helped generate a basis for this review article, it is not my original work, and as such is included in the appendix and not the main document. See

appendix iii) Liu D, Dan M, Adivi N. Blood Conservation Strategies in Total Hip and Knee Arthroplasty. Reconstructive review.

The article highlights the importance of patient specific blood management strategies, aiming to conserve blood in three areas i) pre operatively, ii) intra-operatively, iii) post operatively. Specific mention was made to highlight the importance of identifying and correcting pre-operative anaemia, salvaging peri-operative red cells and the use of tranexamic acid in reducing blood loss. The below table summarizes conservation strategies in these three areas.

Pre-operative	Intra-operative	Post-operative
1. Correcting anaemia a) Iron supplements b) Erythropoietin 2. Pre-operative autologous blood donation 3. Ceasing antiplatelet and anticoagulant medications	1. Acute normovolaemic haemodilution 2. Intra-operative cell salvage 3. Tranexamic acid a) Intravenous b) Topical c) Oral	1. Post-operative cell salvage 2. Re-infusion drain 3. No drain use 4. Tranexamic acid a) Intravenous b) Oral

Blood management strategies are individualised based on each patient and surgeon factors. Therefore, it is up to the surgeon to assess each of their patients and decide how these recommendations best relate to their patients and practice.

Personal development

Doing the masters has helped me develop in a number of ways;

---Personal attributes-

My ability to time manage has significantly improved. Having to manage full time work as a doctor, family commitments and social life while undertaking this masters has been difficult and at times not manageable. I quickly learnt to set myself deadlines and work towards goals. Once I had achieved each goal, I had to quickly reset new ones to make the most of my time.

---Research abilities.

Undertaking the masters has enabled me to participate and understand the process of how to conduct a study. Defining a question, undertaking a literature search and review, study design, gaining ethics approval, data collection, statistical analysis, writing up the research and multiple refinements for publication and presentation. I am now in a position to be more efficient with my time for future research, and by engaging in research, I will be better able to critique other evidence based medicine

---Doctor/surgeon.

Through undertaking research in my chosen field, orthopaedics, I have been able to gain a better knowledge base in the field I want to practice. This has helped with the way I treat my patients by allowing me to practice and advocate for best evidence medicine/surgery.

Conclusion

Arthroplasty, or joint replacement surgery, is increasing in incidence with an ageing population[clxxxi]. An older age is associated with a lower baseline haemoglobin. These are the two highest risk factors for allogenic red cell transfusion in arthroplasty surgery[clxxxii]. Given the number of surgeries are increasing, and the patient group are at increased risk,

measures need to be taken to reduce the overall incidence of red cell transfusion as 1) allogenic blood is a limited resource and 2) allogenic transfusion are associated with a impaired outcomes in the arthroplasty population.

This thesis *What are the optimal methods for reducing blood loss in total joint surgery* sought to better understand this health care challenge. Through the literature review I was able to find additional evidence for recommendations in the national blood authority's perioperative guidelines for blood management[clxxxiii] as it related to arthroplasty and was able identify areas where the recommendations lacked evidence from an arthroplasty perspective, and this formed the basis of the two papers.

Blood loss in primary total knee arthroplasty—body temperature is not a significant risk factor—a prospective, consecutive, observational cohort study? Was the first study to look at temperature and its relationship to blood loss in knee arthroplasty, and contrary to other areas of surgery it was not associated with blood loss in the knee arthroplasty patient. Significantly it was the first study to demonstrate the protective benefit of regional and spinal anaesthesia in preventing blood loss in knee arthroplasty patients.

Analysis of the effectiveness of perioperative cell salvage in primary total hip and knee arthroplasty explored the use of cell saver in the largest cohort of arthroplasty patients in the literature to better define its utility. We identified low haemoglobin(<120) as having he highest odds of transfusion and a high haemoglobin(>150) as having minimal odds of transfusion, and as such are unlikely to need cell saver to prevent transfusion. The amount of blood loss required for red cell salvage to utilize the returned blood is an interaction of the total volume of blood loss and the hematocrit of the blood lost. Paradoxically, anaemic patients pre-operatively have to lose more blood intra-operatively to be able to cell salvage and this could contribute further to low haemoglobin and being at increased risk of transfusion. Therefore we believe those with a hemoglobin of 120-150 are likely to receive

the greatest utility from cell saver and those with a hemoglobin of <120 should undergo measures preoperatively to increase their baseline hemoglobin prior to surgery.

This evidence helps to contribute to formulating a blood management program in patients undergoing arthroplasty to decrease allogenic transfusion rates through pre, intra and post operative measures. Clinicians are encouraged undertake these practices due to the evidence behind it.

As arthroplasty is an elective procedure, we should aim for a zero complication rate. Anaemia due to blood loss is one of the major complications of arthroplasty surgery, additionally to that; blood loss and allogenic transfusion further contribute to other perioperative complications. As addressed by this thesis, all such measures should be taken to minimise this blood loss and allogenic transfusion.

List of tables, figures, diagrams, illustrations

Each of the tables and figures are presented in the respective papers section. They have no independent value and are therefore not represented here.

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Appendix i)

Surgeons

Dr David Liu- involved in both studies.

Dr Ray Randle- involved in only the temperature study involving Total Knee arthroplasty.

Location

Both surgeons operate at the John Flynn private hospital in Tugan on the Gold Coast, Queensland. Near identical operating theatres and similar perioperative staff and protocols, including operating room temperature of 19-20 degrees.

Hip Replacement-

-Only used in the cell saver paper by Dr Liu

Approach- Dr Liu utilises an **anterio-lateral approach** to hip for his total hip arthroplasty. The patient is placed in the lateral position. The skin incision 2.5 cm posterior and distal to ASIS continued distally centred of tip of greater trochanter and continuing over the posterior 1/3rd of the femoral shaft.

-Superficially the fascia lata is split and a plane is developed between gluteus medius and tensor fascia lata

-Deep dissection involves partial splitting of the abductor mechanism . The leg is externally rotated and and anterior capsulotomy is performed to expose the hip joint. Rectus femoris and iliopsoas are reflected off the joint capsule as needed

-The femoral neck is sawed off, acetabulum exposed. The acetabulum is reamed to expose bleeding subchondral bone. The acetabulum shell and cup are then placed in a slightly anteverted(approximately 10^{o}) and abducted position(40^{o}).

-The femoral canal is then broached to appropriate size and femoral neck and head are able to ensure adequate offset and range of motion without risk of impingement or dislocation.

Components: Uncemented acetabular and femoral components were inserted in all patients.

Wounds were closed in a layered fashion, including capsule repair, without use of a drain.

Patients were allowed to *immediately weight bear* post operatively

DVT prophylaxis- All patients received enoxaparin 40mg daily for venous thromboembolic prophylaxis, commencing 4 hours post-operatively and continued for 28 days.

-All patients received mechanical prevention in the form of T.E.D. (Thrombo Embolic Deterrent) stockings and while non-ambulatory sequential compression devices (SCD).

No patient received tranexamic acid, as these studies were carried out prior to its routine use.

Knee replacement

-Utilized by both surgeons.

Approach: Both surgeons utilise a medial parapatellar approach, with the patient in the supine position. The skin incision is midline proximal to the patella, across its midline, down the medial aspect of the tibial tubercle.

Superficial dissection involves incising and reflecting subcutaneous fat and deep fascia.

Deep dissection involves splitting between vastus medialis and vastus intermedius tracing distally 1-2cm medial to the patella tendon through the retinaculum to expose the joint,

down to the medial side of the tibial tubercle. The patella tendon is inverted and retracted laterally to expose the joint.

Dr Liu utilises *computer navigation* for femoral and tibial *bone cuts* and component position where as Dr Randle utilises *intramedullary instrumentation* for femoral and tibial bone cuts.

Components- Both surgeons resurface the patella in all cases

Tourniquet- is not used by either surgeon

Wounds were closed in a layered fashion with the use of an intra-articular drain removed day 1 post operatively in all cases by both surgeons.

Both surgeons allowed patients *to weight bear immediately* post operation.

DVT prophylaxis- Dr Liu- All patients received enoxaparin 40mg daily for venous thromboembolic prophylaxis, commencing 4 hours post-operatively and continued for 14 days.

-Dr Randle- all patients received rivaroxaban 10mg daily initiated 6 hours post operation and continued for 14 days.

Aspirin was continued in those patients on it pre operatively along with enoxaparin or rivaroxaban. Patients on warfarin preoperatively were continued on this as the choice of chemical DVT prophylaxis at a perioperative INR of 2.2.

All patients received mechanical prevention in the form of T.E.D. (Thrombo Embolic Deterrent) stockings and while non-ambulatory sequential compression devices (SCD).

No patient received tranexamic acid, as these studies were carried out prior to its routine use.

Observations and investigations

Routine 6 hourly observations were utilized for the temperature study. As this study was observational no change was needed. Temperature was measured using axillary temperature.

Total drain volume was routinely measured by nursing staff and translated to post operative blood loss in knee replacement patients

Routine Blood tests including a full blood count and electrolytes was routinely carried out within 2 weeks prior to the operation and day 1 following the operation. This allowed a pre operative vs post operative difference in haemoglobin to be calculated correlating with total blood loss.

Anaesthetic agents-

Where possible regional block(femoral) and spinal were utilised in combination with a general anaesthetic or sedation. Patient preferences, comorbidities or failed attempts at spinal lead to different combinations regional, general and spinal being utilised. These were recorded

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RESEARCH ARTICLE Open Access

Warfarin cessation is non-essential in patients undergoing total knee arthroplasty—a case-control study

Alfred Phillips[1*], Michael Dan[2], Nathan Schaefer[1] and Raymond Randle[3]

Abstract

Background: Warfarinised patients frequently present for total knee arthroplasty (TKA). Current practice of heparin 'bridging' is potentially cumbersome and hazardous. The research question is if cessation of warfarin is necessary for TKA.

Methods: The study design was a retrospective case–control series of 61 warfarinised patients and 61 control patients undergoing TKA. TKA was performed by the senior author using a medial parapatellar approach without tourniquet. The target perioperative international normalised ratio (INR) for warfarinised patients was 2–2.2. Primary outcomes were changes in haemoglobin, transfusion requirements and complication rates.

Results: There was no statistically significant difference between control and warfarin group in mean perioperative Hb (g/L) (pre-op 140 vs 141, day 0 115 vs 115, day 1 108 vs 111, $P = 0.63$), transfusion rates (14.75% vs 9.83%, $P = 0.58$), total complication rate (9.8% vs 9.8%, $P = 0.75$), demographics, range of motion or length of stay. There was a statistically significant higher use of the re-infusion drain in the warfarinised group (47.5% vs 24.6%, $P = 0.014$).

Conclusion: This study supports the hypothesis that warfarin cessation is non-essential in patients undergoing TKA. This data is applicable to a patient group using re-infusion drains. Limitations of this study are typical of a small non-controlled observational study.

Keywords: Total knee arthroplasty, Anticoagulation, Warfarin, Continuation, Cessation, Bridging, Complications

Introduction

Total Knee arthroplasty (TKA) is a reliable treatment for end-stage arthritis. Osteoarthritis is the main aetiology of arthritis requiring TKA [1]. The incidence of osteoarthritis increases with age as do the relative comorbidities of the patient [2]. Common comorbidities include atrial fibrillation, venous thrombosis and valve replacement and these commonly require anticoagulation therapy, traditionally warfarin [3]. The Australian National Joint registry data demonstrates a 4.1% increase in TKA in 2012 from 2011 and a 92.4% increase since 2003 [1]. This is in keeping with a worldwide trend [4,5]. With an ageing population and a corresponding increase in the incidence of TKA, it is safe to assume an increasing proportion of patients who present for TKA will be on warfarin.

Warfarin exerts its anticoagulant affect as a vitamin K antagonist that inhibits clotting factors 2, 7, 9 and 10. This results in increased prothrombin time via impaired formation of fibrin. Conversely, proteins C and S are inhibited, which provides an initial pro-thrombotic effect. Warfarin is variably metabolised by the liver subject to patient factors such as genetics, diet and medications. The therapeutic window of warfarin is monitored via the international normalised ratio (INR). It has a half life of approximately 36 hours [6].

To manage the increased bleeding risk in patients undergoing TKA, warfarin is traditionally stopped 5 days pre-operatively. Patients are then assessed into low- and high-risk categories, with bridging anticoagulation in the form of low molecular weight heparin or unfractionated heparin recommended for higher risk patients [7].

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The cessation of anticoagulation has been associated with a 1%–3% incidence of cerebrovascular events in specific populations of patients, resulting in significant morbidity and mortality [8,9]. There is also the concern that a rebound hypercoagulability on cessation can lead to increased risk of thrombotic events due to re-initiating warfarin [10,11]. Bridging therapy increases post-operative stay and healthcare costs as warfarin is restarted [12]. Recently, Simpson et al. found that bridging anticoagulation therapy for warfarinised patients undergoing TKA was associated with an increased risk of prolonged wound drainage, superficial infection, deep infection, washout and revision surgery [13].

In an effort to decrease risks and costs, studies have explored the safety of continuing warfarin perioperatively [9,14-17]. Rhodes et al. [18] and Chana et al. [19] suggest that cessation of warfarin perioperatively in patients undergoing TKA is unnecessary. These retrospective case–control studies including 38 and 24 patients in each group, respectively, are limited by low numbers. Our aim was to expand upon current literature and show that warfarin can be continued safely and effectively within its therapeutic range in patients undergoing TKA.

Methods

The study design was a retrospective observational case–control series that required low-risk ethics approval and relevant data was obtained from the Health Information Services Unit. The senior author (RR) maintains lists of all his patients undergoing procedures while on any form of anticoagulation. The hospital reference numbers of the patients that underwent TKA while remaining on warfarin were used to locate charts and gather de-identified data. Data was extracted from inpatient notes, pathology, and operation and anaesthetic reports.

The inclusion criteria for the warfarin group of the study were long-term warfarinised patients (minimum of 6 months duration with stable INR) who underwent TKA by the senior author. No patients were excluded due to increased bleeding risk, high BMI, more complex TKA or at high risk of complications from general anaesthesia during the study period. Sixty one warfarinised patients were included in the study. The target INR range for the warfarinised group was 2–2.2 on the day of surgery. A total of 61 age- and gender-matched control subjects were chosen from the senior author's booking diary during the same time period as the study group. The only information visible in the diary was the control patient's name, date of birth and hospital reference number. The control subject age range was 6 months older or younger than the study subject. Patients were not matched for BMI but there was no statistically significant difference in BMI (29.7 kg/m^2 for the control group vs 30.9 kg/m^2 for the warfarin group ($P = 0.23$). Inclusion criteria for control subjects were age- and gender-matched patients undergoing TKA who were not on warfarin.

The study period included a consecutive cohort of warfarinised patients undergoing TKA from the time the senior author initially used this method of perioperative anticoagulation up the time of data collection. All warfarinised patients were on warfarin as lone anticoagulation. Six control patients were on aspirin for primary prevention of cardiovascular disease prior to surgery. Aspirin was ceased in all of these patients pre-operatively. All non-steroidal anti-inflammatory drugs were ceased 7 days pre-operatively in both study groups to optimise renal perfusion.

All warfarinised patients received a general anaesthetic. Control patients either received general or spinal anaesthetic informed by the anaesthetist and patient preference. All 122 patients were implanted with DePuy PFC implants between 2010 and 2013. With meticulous haemostasis, a medial parapatellar approach was used without tourniquet (not inflated at any stage during the procedure). All wounds were closed in 'water-tight' layers with the knee flexion with interrupted polydioxanone (PDS) and Monocryl to skin. There was no use of tranexamic acid (TXA), bipolar sealers or any other haemostatic techniques besides electrocautery during surgery. This cohort of patients was from a period before TXA was in mainstream use. All patients had re-infusion drains inserted intraoperatively and standardised pathology collected. All drains were removed day 1 post-operatively. All patients were able to full weight bear immediately post-operatively and underwent a standardised physiotherapy rehabilitation protocol commencing day 1 post-operatively. The senior author made all decisions regarding post-operative transfusion using the National Health and Medical Research Council (NHMRC) transfusion guidelines depending on the volume of the blood loss, fluid status, Hb concentration and the patient's clinical condition. Patients who were symptomatically anaemic with Hb of <80 or <100 g/L in those with a documented history of end-organ atherosclerotic disease (i.e., ischaemic heart disease, chronic renal failure) were transfused red blood cells.

Warfarin dosing in the warfarin group was titrated using INR in an attempt to achieve a perioperative range of 2–2.2. The INR was checked within 48 h pre-operatively in all warfarinised patients. Patients were counselled pre-operatively about the effects of diet on INR and encouraged not to make any significant changes to their diet perioperatively. Patient diet was not formally modified or monitored at any stage of care. Control subjects were commenced on rivaroxaban (10 mg once daily) as a lone anticoagulation agent in the immediate post-operative period. All patients used the same mechanical venous thromboembolism (VTE) prophylaxis while inpatients.

All patients received a standardised pre-operative assessment including basic blood tests and coagulation profiles by the senior author. Standardised post-operative outcome data from clinical reviews at 2 weeks, 6 weeks and 6 months were used to assess medium-term outcomes for all patients. The minimum length of follow-up for the study was 6 months. This timing corresponded to when patients were first discharged back into the care of their local doctor. The average follow-up was 8.5 months for the study group (range 6 to 15 months) and 9 months for the control group (range 6 to 13 months). All outcomes and adverse events were included up until the time of discharge or if the patient was seen again for a related matter on an 'as needed' basis.

Statistical analysis was performed using SPSS version 21 for Windows (SPSS Inc., Chicago, IL). Variables were summarised by the mean, standard deviation (SD), 95% confidence intervals or frequency. Chi-square tests were used to compare categorical variables. Independent sample *T* tests were used to compare quantitative variables for two groups. A repeated measures analysis of variance (ANOVA) was performed to test the hypothesis that warfarin is associated with different Hb levels across time compared to controls. Statistical significance was set at $P < 0.05$ for all tests. A post hoc power analysis was performed with observed values from the data collected. The sample size used in this study ($n = 61$ in each group) yielded approximately 8% power to detect the effect size 0.2% as being statistically significant ($P < 0.05$). This was based on a mean of 108 g/L (SE = 1.7) in controls and a mean difference of ~2.6 g/L between control and study group at day 1.

Results

There was no statistically significant difference in patient age, gender or pre- and post-operative range of motion between the warfarin and control groups. There was no statistically significant difference in BMI between the two groups (29.7 kg/m^2 for control group vs 30.9 kg/m^2 for the warfarin group, $P = 0.23$). There was no statistically significant difference in surgical time between the two groups. The mean operative time for the control group was 56 min vs 54 min for the warfarin group ($P = 0.31$). The mean pre-operative INR in the warfarinised group was 2.0 (range 1.9 to 2.3). The most common indication for warfarinisation of patients in this study was a history of atrial fibrillation and venous thromboembolism shown in Table 1.

There was no statistically significant difference between the control and warfarin group in the mean perioperative haemoglobin (pre-op 140 vs 141 g/L, day 0 115 vs 115 g/L, day 1 108 vs 111 g/L $P = 0.63$) as shown in Figure 1.

Table 1 Frequency distribution of indications for warfarinisation

Indication for warfarin in the study group	Number (%) of the study group
History of atrial fibrillation	33 (54.1)
Previous venous thromboembolism	17 (27.9)
Cerebrovascular accident	3 (4.9)
Myocardial infarction	2 (3.3)
Valvular heart disease	2 (3.3)
Severe peripheral vascular disease	1 (1.6)
Paroxysmal atrial arrhythmia and pacemaker	1 (1.6)
Mechanical heart valve	1 (1.6)
Ischaemic heart disease	1 (1.6)

There was no statistically significant difference in total transfusion rates (14.75% vs 9.83%, $P = 0.58$) as shown in Table 2.

There was a statistically significant higher use of the re-infusion drain in the warfarinised group (47.5% vs 24.6 %, $P = 0.014$) as shown in Table 3. The mean INR for the warfarin group was 2.0 pre-operatively, 2.5 on days 1 and 2 and 2.3 on day 3 post-operatively.

There was no statistically significant difference in the total complication rate (9.8% vs 9.8%, $P = 0.75$). A warfarinised, immunosuppressed, morbidly obese patient with rheumatoid arthritis developed a septic TKA. Pre-operative counselling addressed her significantly increased risk of infection. She underwent two-stage revision and made a full recovery with a range of motion of 0°–105°.

A warfarinised patient was re-admitted day 14 post-operatively with a haemarthrosis secondary to a supra-therapeutic INR of 8. The haemarthrosis was treated conservatively with ice and elevation while his INR was corrected. He was discharged day 3 post re-admission and made a good recovery with a range of motion of 10°–115°.

A warfarinised patient with a history of lower gastrointestinal tract bleeds was re-admitted day 8 post-operatively with malaena and Hb of 78 g/L. The patient was transfused two units of packed red bloods cells and four units of fresh frozen plasma. An upper endoscopy and colonoscopy did not identify the source of bleeding. The malaena resolved and the patient made a good functional recovery with a range of motion of 3°–110°.

A warfarinised patient with long-standing mild cognitive impairment fell out of bed during an episode of acute confusion post-operatively. They sustained a superficial wound dehiscence that required closure under general anaesthetic. The wound healed well; however, poor compliance post-operatively limited recovery, resulting in a range of motion of 45° to 105°.

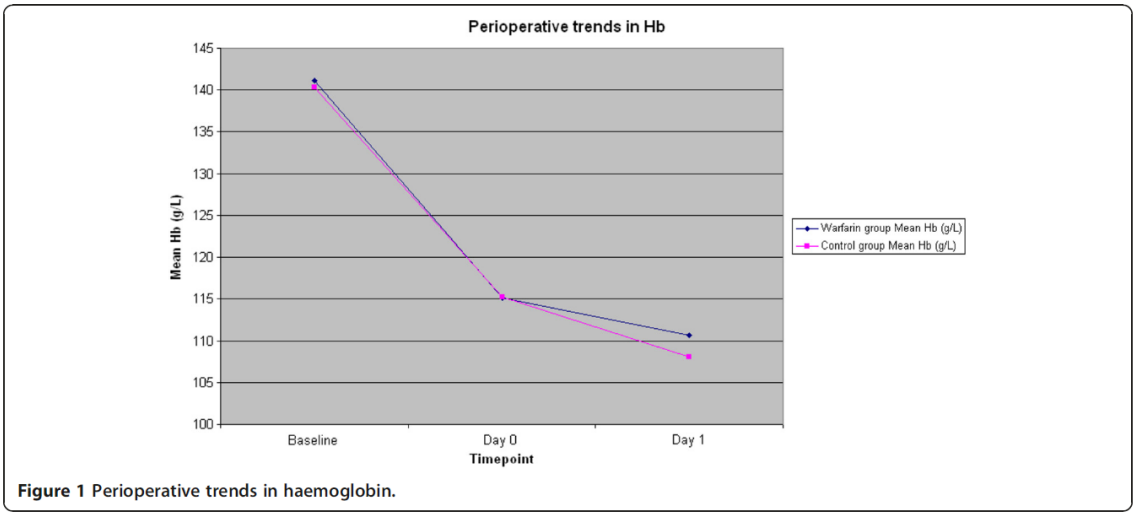

Figure 1 Perioperative trends in haemoglobin.

A warfarinised patient with a history of ischaemic heart disease suffered a non-ST elevated myocardial infarction (NSTEMI) day 3 post-operatively in the setting of analgesic nephropathy. The patient was treated with a GTN infusion and PCI where they were found to have 50% stenosis of their left anterior descending (LAD) coronary artery. A good functional recovery achieved a range of motion 0°–115°.

A warfarinised patient with an extensive past medical history of cardiovascular events suffered a TIA post-operatively. A carotid Doppler ultrasound showed a 50%–69% carotid stenosis. The patient was treated conservatively and made a good recovery with a post-operative range of motion of 20°–105° (pre-operative ROM 20°–95°).

A control patient was readmitted 3 weeks post-operatively with a 3-day history of malaena and haemoglobin of 77 g/L. The patient underwent endoscopy and was found to have duodenal erosions. The patient was transfused three units of packed red blood cells. The patient recovered well and achieved a range of motion of 5°–90°.

A control patient developed anaemia unresponsive to a total of six units of packed red bloods cells. The patient had a history of severe peripheral vascular disease, left below-knee amputation (BKA), polymyalgia rheumatica on oral steroids and chronic obstructive pulmonary disease (COPD) on home oxygen. Day 7 post-operatively, the patient underwent gastroscopy that identified distal gastritis that was treated with a proton pump inhibitor. The patient also developed bilateral pulmonary emboli on CT pulmonary angiogram at 8 weeks post-operatively. The patient was treated with aspirin and warfarin (with LMWH bridging). The patient had significant hamstring spasm and compliance issues post-operatively with a range of motion of 45°–100°. At last

Table 2 Post-operative transfusion requirements

	Control group ($n = 61$)	Warfarin group ($n = 61$)	*P* value
Number of PRBCs transfused during admission			
0	53	55	
1	1	0	
2	6	3	
3	1	1	
4	0	1	
5	0	1	
6	1	0	
Total % of patients requiring transfusion of PRBCs	14.75%	9.83%	$P = 0.58$
Total number of units PRBCs transfused	21	14	

Table 3 Post-operative use of re-infusion drains

	Control group ($n = 61$)	Study group ($n = 61$)	*P* value
Volume re-infused via Stryker re-infusion drain (mL)			
0	46	32	
100–200	1	6	
200–300	8	9	
300–400	4	7	
400–500	1	3	
500–600	0	2	
600–700	0	2	
700–800	0	0	
800–900	1	0	
Use of re-infusion drain (%)	24.6	47.5	$P = 0.014$

review, the patient declined to undergo manipulation under anaesthesia.

A control patient suffered a superficial wound dehiscence while flexing their knee day 3 post-operatively. The wound was closed under local anaesthetic and healed well. The patient made a good functional recovery with a range of motion at 0°–110°.

A control patient suffered a seizure in the immediate post-operative period in the recovery suite. The patient likely received an inadvertent intravenous dose of local anaesthetic for a regional block by the anaesthetic team. The patient had no hypotension or signs of decreased cardiac output. They received 5 mg of intravenous midazolam, which resulted in immediate cessation of seizure activity. The patient was transferred to the intensive care unit for observation and discharged to the general orthopaedic ward day 2 post-operatively with no long-term sequelae. The patient made a good post-operative recovery with a range of motion of 5°–110°.

A control patient developed post-operative confusion secondary to anaemia day 3 post-operatively. The patient had a normal CT head and a negative septic screen. They received three units of PRBCs and had a good long-term outcome with a range of motion of 5°–100°.

Discussion

The results of this study support the hypothesis that cessation of warfarin in patients undergoing total knee arthroplasty is not necessary. Warfarin continuation was shown to be a safe and effective way of anticoagulating patients perioperatively. Two other studies (Rhodes et al. and Chana et al.) have investigated the continuation of warfarin in patients undergoing TKA [18,19].

Rhodes et al. and Chana et al. found no increase in the rate of haemorrhage for patients on continuous warfarin. In our study, of 61 warfarinised patients undergoing TKA, the mean pre-operative INR in the warfarinised group was 2.0 with a mean increase of 0.3 by day 3 post-operatively. The senior author designated the optimal perioperative INR range of 2–2.2. Chana et al. reported similar results with a mean pre-operative INR of 2.2 and a mean change in INR of 0.4 [19]. Rhodes et al. also reported a mean pre-operative INR of 2.1 and a mean change in INR of 1.2 [18].

There was no statistically significant difference in perioperative haemoglobin and total complication rates between warfarinised and control patients in our study. Both Chana et al. and Rhodes et al. also found that there was no statistically significant difference in complication rates in warfarinised patients undergoing TKA [18,19]. None of the warfarinised patients in our study suffered any embolic events such as VTE or CVA.

No statistically significant difference in the transfusion requirements of the two groups was demonstrated with 9.8% of warfarinised patients and 14.8% of control patient requiring blood transfusions. Both Chana et al. and Rhodes et al. also found that there was no statistically significant difference in transfusion requirements in warfarinised patients undergoing TKA [18,19].

All patients in our study had a closed suction drain that was combined with a collection-re-infusion system for post-operative blood recovery (Stryker CBCII). We chose to include this data due to the oxygen carrying capacity of the drain contents. Several studies have highlighted the merit of these systems in successfully decreasing allogenic transfusion requirements in total joint arthroplasty [20-24]. There was a statistically significant increase in autotransfusion requirements of warfarinised patients in our study. This was a significant finding given that there was no difference in perioperative Hb between the two groups. We recommend that our data is applicable to warfarinised patients undergoing TKA using a similar drain.

In our study, warfarinised and control patients were age- and gender-matched. Patient BMI and pre- and post-operative range of motion was recorded. There was good homogeneity of patient demographics between the two groups. There was no statistically significant difference in pre- and post-operative range of motion. The majority of patients in our study were warfarinised for either atrial fibrillation (AF) or previous VTE. In the setting of untreated AF, data from the Framingham studies has shown a 28.2% risk of CVA over an 11-year period [25]. Warfarinised patients with a history of transient ischaemic attack, diabetes or ischaemic heart disease have even greater risk of stroke when not anticoagulated [26]. Despite these risks, the American College of Cardiology maintain that warfarin can be ceased for up to a week without bridging for procedures that carry a risk of haemorrhage [27]. The group, along with most surgeons, advocate for individualised risk stratification when determining the most effective form of perioperative anticoagulation in this patient population [28].

A recent study by Simpson et al. has highlighted the increased incidence of post-operative complications when warfarinised patients are bridged with another agent for TKA [13]. In this study, 149 patients on warfarin pre-operatively were bridged with either low- or high-dose unfractionated heparin, low- or high-dose low molecular weight heparin, IV heparin or aspirin. There were significantly higher complication rates in this patient group compared to the control group with the bridged group at particularly high all-cause risk [1.8, (95% CI 1.15 to 2.35), $P = 0.001$]. There was also a significant higher incidence in prolonged wound drainage (26.8% of cases vs 7.3% of controls, $P = 0.001$); superficial infection (16.8% vs 3.3%, $P = 0.001$); deep infection (6.0% vs 0% $P = 0.001$); return-to-theatre for washout (4.7% vs 0.7%, $P = 0.004$) and

eventual revision (4.7% vs 0.3%, $P = 0.001$). The limitations of the study by Simpson et al. were multiple contributing surgeons, the type of thromboprophylaxis in the control group was not standardised, the use of tourniquets and drains was not standardised and there was no uniform transfusion protocol. Despite these limitations, the findings by Simpson et al. are in keeping with our anecdotal experience and difficulty with bridging warfarinised patients. This prompted the senior author to first consider continuing his patients on warfarin perioperatively. There are currently two large multi-centre randomised control trials PERIOP 2 and BRIDGE assessing whether post-operative bridging reduces risk of VTE or increases morbidity.

The limitations of this study are typical of small, non-controlled, retrospective, observational studies. The number of warfarinised patients was low, which resulted in the study being relatively underpowered and the statistics described are susceptible to type II error. The recruitment of these patients was passive and therefore difficult to increase. The authors acknowledge that, despite being age- and gender-matched, the control subjects were manually selected from an operative diary. The senior author's practice does not use electronic records, which made it difficult to overcome this issue. We also acknowledge that complications were compared as a total complication rate and we did not account for the severity of individual complications. The decision to continue warfarin perioperatively precludes patients from undergoing spinal anaesthesia due to the risk of epidural haematoma. The senior author has not had to cease warfarin for any patients undergoing TKA. Despite being the largest series of warfarinised patients undergoing TKA, our data does not provide sufficient evidence to recommend cessation of warfarin pre-operatively in more complex cases such as revision surgery. We recommend that all patients with increased but reducible perioperative risk should be medically optimised. While there are no absolute contraindications to general anaesthesia, valvular heart disease is a common contraindication to regional anaesthesia for which many patients are warfarinised. Current literature suggests that there is no increased risk of mortality, cardiac complications or VTE between spinal and general anaesthesia [29-31].

The strengths of this study are that it has a simple design and it is the largest published cohort of warfarinised patients undergoing TKA. It was a single-centre, single-surgeon study. All patients received the same implants and the senior author made all clinical decisions.

Conclusion

The primary consideration for surgeons planning to perform TKA on chronically warfarinised patients is balancing the risks of thromboembolism against post-operative complications. This is challenging. In an attempt to mitigate risk of complications, patients have traditionally had warfarin withheld pre-operatively and bridged with a shorter acting form of anticoagulation. This strategy is potentially perilous for the patient and cumbersome for the clinician. In conclusion, the authors feel that continuation of warfarin is a safe and effective form of perioperative anticoagulation in patients undergoing TKA. Re-infusion drains should be used on warfarinised patients undergoing TKA. While acknowledging the limitations of this study, the findings contribute to the discrete body of literature that supports the notion that warfarin cessation is non-essential in patients undergoing total knee arthroplasty with concomitant use of a re-infusion drain.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AP is the lead author responsible for study design, data collection, analysis and interpretation and critically appraised manuscript for submission. He has given approval of final version to be published and is accountable for all aspects of work at the highest standard. MD and NS are the later authors responsible for data collection, analysis and interpretation and critically appraised manuscript for submission. They have given approval of the final version to be published and are accountable for all aspects of work at the highest standard. RR is the senior author responsible for study design, analysis and interpretation and critically appraised manuscript for submission. He has given approval of final version to be published and is accountable for all aspects of work at the highest standard. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Blood Conservation Strategies in Total Hip and Knee Arthroplasty

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Abstract

Peri-operative blood management is one of a number of components important for successful patient care in total joint arthroplasty and surgeons should be proactive in its application. The aims of blood conservation are to reduce the risks of blood transfusion whilst at the same time maximizing haemaglobin in the post-operative period, thereby leading to a positive effect on early and long term outcomes and costs. An individualized strategy based on patient specific risk factors, anticipated blood loss and co-morbidities is useful in achieving this aim. Multiple blood conservation strategies are available in the pre-operative, intra-operative and post-operative periods and can be utilised either individually or in combination. Recent literature has highlighted the importance of identifying and correcting pre-operative anaemia, salvaging peri-operative red cells and the use of tranexamic acid in reducing blood loss. Given total hip and knee arthroplasty is an elective procedure, a zero allogenic blood transfusion rate should be the aim and an achievable goal.

Introduction

One of a number of critical components for successful patient care in joint arthroplasty surgery is a blood management strategy. Hip and knee arthroplasty can result in substantial peri-operative blood loss, rendering the patients at increased risk of requiring a blood transfusion [1,2]. Total joint arthroplasty and fracture surgery is the number one reason for transfusion in patients undergoing surgery and accounts for 9.8% of all transfused red blood cell units [3]. Complications of allogenic blood transfusion include the risk of disease transmission, haemolytic reactions, fluid and haemodymanic overload, acute lung injury, coagulopathy, allergic reactions and febrile non-haemolytic reactions [4]. There is evidence that allogenic transfusions are associated with immunomodulation, and an increased incidence of infection [5]. Bierbaum reported transfusion rates of 57% for total hip arthroplasty (THA) and 39% for total knee arthroplasty (TKA), with an increased risk of fluid overload, infection rate and duration of hospitalization in the patients who received allogenic transfusion [6]. Several studies have highlighted the disadvantages of allogenic blood including a negative effect on postoperative complications, length of hospital stay, cost and mortality [7,8,9].

The fundamental aim of a blood management strategy is to eliminate the need for allogenic blood whilst at the same time preventing anaemia. Thereby the risks of transfusion are removed, haemaglobin (Hb) status is maximized and this leads to a positive effect on the patient's recovery and early and long-term outcomes. Such a strategy should be individualized and based on patient specific

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risk factors including pre-operative Hb level, anticipated difficulty of the procedure and blood loss, and associated medical co-morbidities. Haemaglobin loss in routine primary THA has been calculated to be 4.0g/dL and in TKA to be 3.8g/dL [10]. The ultimate transfusion trigger should also be individualized based on the risks and benefits for each patient. Multiple strategies, used either in isolation or combination, are available to reduce the need for allogeneic blood in joint arthroplasty patients. Available strategies can be broadly divided into 3 stages: pre-operative assessment and optimisation, intra-operative and post-operative protocols [11]. These are summarized in table 1.

Table 1. Summary of blood management interventions available to reduce allogenic transfusion rates in THA and TKA patients.

Pre-operative	Intra-operative	Post-operative
Correcting anaemia - Iron supplements - Erythropoietin	Acute normovolaemic haemodilution	Post-operative cell salvage
Pre-operative autologous blood donation	Intra-operative cell salvage	Re-infusion drain No drain use
Ceasing antiplatelet and anticoagulant mediactions	Tranexamic acid - Intravenous - Topical - Oral	Tranexamic acid - Intravenous - Oral

Pre-operative Strategies

Predicting the risk and need for transfusion pre-operatively has been shown to be an important element of an effective blood management program in joint arthroplasty surgery. Several studies have highlighted the significant influence of pre-operative Hb on the requirement for transfusion in total joint arthroplasty [10,12]. Salido et al demonstrated that very few patients with Hb greater than 150g/L pre-operatively required allogenic blood whilst patients with pre-operative Hb level less than 110g/L had a 100% transfusion rate [12]. Similarly, Pierson et al showed that an algorithmn based strategy aimed at improving pre-operative Hb level was the most effective in reducing transfusion rate [10]. Other risk factors associated with an increased need for transfusion include weight, age greater than 75 years, male gender, hypertension and body mass index less than 27 [13]. Whilst many of these factors are non-modifiable, Pola showed having more than one risk factor had a compounding effect on transfusion rate [14]. Therefore in patients with multiple risk factors, it is vitally important to correct anaemia and maximize pre-operative Hb. Correcting anaemia not only reduces the risk of allogenic transfusion but also has a positive impact on the patient's rehabilitation and functional recovery. Patients with post-operative Hb of between 8 to 10 g/dl may not be low enough to warrant transfusion but often feel lethargic, with a higher risk of syncopal episodes, impairing their ability to mobilize and undergo their rehabilitation.

In order to correct pre-operative anaemia, the cause needs to be fully investigated and corrected as necessary. A common reason, especially in the elderly arthroplasty patients, is iron deficiency due to a combination of poor dietary intake and peptic disease secondary to NSAID use. The typical pattern seen in these patients is low Hb, with a low ferritin. In our centre, patients are screened 3 months prior to surgery with full blood count, proceeding to iron studies if the pre-operative Hb is less than 120g/dL. The parameters measured to investigate pre-operative anaemia are listed in table 2 with the minimum cut-off values. Any patient who is identified as anaemic is referred to the haematology unit for further investigation and management.

***Table 2.** Pre-operative iron studies and critical values used at our institution for patients with pre-operative anaemia requiring correction prior to THA and TKA.*

Parameter	Critical Value
Haemaglobin	12 g/dL
Haematocrit	0.38
Iron	5 μmol/L
Total Iron Binding Capacity	45 μmol/L
Transferrin Saturation	20 %
Ferritin	50 μg/L
Vitamin B12	150 pmol/L
RBC folate	150 nmol/L

The options for maximizing Hb in preparation for surgery include iron supplements or erythropoietin. Iron supplements can either be given orally or intravenously. Both have been shown to be effective however oral iron may not be efficacious in patients with malabsorption such as coeliac disease. Another disadvantage of oral iron supplements is the slow effect and therefore it needs to be implemented well in advance of surgery. A cohort study of 156 patients treated with ferrous sulphate 256mg / day in with combination vitamin C which enhances iron absorption, for 1 month preoperatively showed reduced a transfusion rate for non anemic patients [15]. For our patients with deficient iron stores, the haematologists administer 500-1000mg ferritin carboxymaltose as an intravenous infusion over 15 minutes. Dosage depends on the duration and severity of iron deficiency. The infusion needs to be given a minimum of 3 weeks pre-operatively to enable enough time for red blood cells to regenerate.

Erythropoeitin is a synthetic hormone, which stimulates progenitor cells in the bone marrow to differentiate into red blood cells and thereby stimulating haematopoi-

esis. Erythropioetin is definitely a powerful agent in correcting anaemia and extremely effective in reducing allogenic blood requirement in joint replacement surgery. In a systematic review, Spahn [16] showed erythropoietin to be successful in improving mean preoperative Hb and post operative Hb with reduced transfusion rates when combined with iron therapy in patients undergoing orthopedic operations including hip fracture surgery, THA and TKA. Its main disadvantage remains cost and at this stage, its routine use in Australia is not approved in the joint replacement patients unless the patient suffers from anaemia secondary to chronic renal failure.

A large part of blood conservation in surgery is aimed at limiting blood loss. Patients undergoing THA and TKA frequently take antiplatelet and anticoagulant medications that affect the risk of bleeding. The decision and timing of cessation of antiplatelelet and anticoagulant therapy needs to take into consideration the risks of thrombosis versus the risk of bleeding. Platelet activation occurs with non-cardiac surgery, making myocardial infarction the most common major vascular complication after surgery. Under usual circumstances, warfarin should be discontinued 5 days prior to arthroplasty surgery [17] and recommenced postoperatively when the risks of acute bleeding are believed to be stable. Bridging anticoagulation therapy is commonly used in the interim period with agents such as low molecular heparin, which have a shorter half-life [18]. There are no clear guidelines or consensus on the optimal bridging therapy for patients on warfarin for conditions such as atrial fibrillation, previous embolic cerebrovascular events or mechanical valve replacement and further clinical trials are required to clarify the optimal regime.

With regards to aspirin and antiplatelet therapy, its cessation prior to surgery is believed to result in an increased risk of cardiovascular complications and major cardiac events [19,20]. However a recent large randomized controlled trial of 10010 patients of which 39% underwent orthopaedic procedures, comparing aspirin versus placebo with 30 days follow up after surgery, found conflicting results [21]. There was no difference in the primary outcome of death or myocardial infarction between the 2 groups, regardless of whether the patient was taking aspirin prior to surgery or not. Aspirin increased the risk of major bleeding compared with placebo. The most common reported site of bleeding were the surgical site in 78.3% and gastrointestinal tract in 9.3%. The authors concluded aspirin administration before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding. We now cease aspirin prior to THA and TKA.

Once popular in elective joint replacement surgery was pre-operative autologous donation. Autologous donation has been demonstrated to be effective in reducing allogenic blood requirements. Allogeneic transfusion rates were reduced from 40%, 52% and 91% in the non-preoperative autologous donation group to 3%, 18% and 9% respectively in the preoperative autologous donor group in three cohort studies [22,23,24]. However pre-operative autologous donation is associated with a high rate of wasted blood units and is no longer deemed to be cost effective. There remains the potential for the wrong blood being returned to the patient due to clerical errors [25,26]. The process itself necessitates the inconvenience of having to donate blood in advance of scheduled surgery. The Australian Blood Bank as a consequence currently imposes a cost to patients if they wish to utilize this service. The use of preoperative autologous blood donation has therefore fallen out of favour.

Intra-operative Strategies

A major element of intra-operative blood management is limiting the amount of blood loss. The risk of bleeding depends on the difficulty of the procedure and patient risk factors such as obesity, co-morbidities and bleeding disorders. Regardless of what additional strategies are incorporated, maintaining steady blood pressure and normothermia are both recommended in reducing blood loss. Crucial to blood loss management is meticulous efficient surgical technique with careful dissection, soft tissue handling and bleeding control.

The technique of acute normovolaemic haemodilution attempts to achieve a similar effect to pre-operative autologous blood donation but without the inconvenience of preoperative donation. Blood is collected from the patient in the immediate pre-operative period and volume is replaced with colloid or crystalloid fluid. The rationale behind the technique is surgical blood loss will have a lower haematocrit. The pre-operatively collected whole blood is transfused in the immediate post-operative period negating the downsides of blood storage. However the effectiveness of acute normovolaemic haemodilution in reducing transfusion need is debatable [16]. Its use may be appropriate in selected cases where cross matching of blood is difficult due to the presence of antibodies.

Peri- operative red cell salvage is another strategy available to minimize the effects of blood loss following total hip and knee arthroplasty. Blood lost during the operative procedure and immediate post-operative period can be salvaged and returned to the patient. This technique has sev-

eral advantages over the previously described methods of pre-operative autologous donation and acute normovolaemic haemodilution. Peri-operative red cell salvage re-infuses fresh blood and avoids the problems with storage of red blood cells seen with autologous pre-donation and allogeneic red blood cells. This translates to more efficacious oxygen carrying red blood cells with a higher mean erythrocyte viability [27] and increased preservation of 2-3 diphosphoglycerate [28]. The technique also incorporates washing the blood loss volume. Washing the blood removes biochemical, cellular and non-cellular debris [29]. Unwashed cell salvage has been associated with adverse post-operative effects due to the presence of cytokines including hypotension, hyperthermia, increased postoperative bleeding and non-cardiogenic pulmonary edema. [30, 31] We have been using intra-operative red cell salvage in our unit for the past 4 years for primary and revision hip and knee replacement. An audit of our transfusion rates in comparison to other studies in the literature is listed in table 3 for THA [32,33,34] and table 4 for TKA. [35,36,37] Peri-operative red cell salvage definitely reduces but does not eliminate the need for allogenic blood, especially in patients who have a low baseline haemaglobin pre-operatively.

Table 3. Effects on Allogenic Transfusion Rates of autologous retransfusion of salvaged blood cells in randomized controlled trials and cohort studies for THA compared to historical rate reported by Bierbaum without intervention.

Study	Bierbaum [6]	del Trujilo [32]	Smith [33]	Moonen [34]	Our Data
Allogenic Transfusion Rate	57%	15%	8%	6%	23.7%

Table 4. Effects on Allogenic Transfusion Rates of autologous retransfusion of salvaged blood cells in randomized controlled trials and cohort studies for TKA compared to historical rate reported by Bierbaum without intervention.

Study	Bierbaum [6]	Shenolikar [35]	Thomas [36]	Munoz [37]	Our Data
Allogenic Transfusion Rate	39%	16%	7%	11%	11.9%

Post-operative Strategies

The routine use of intra-articular wound drainage in THA and TKA has been shown to increase blood transfusion requirement [38]. This needs to be balanced with the reported increased risk of persistent ooze, bruising and haematoma formation [39]. The evidence for use of an intra-articular drain therefore remains inconclusive and very much an individual decision based on surgeon preference.

Post-operative reinfusion drains are also commonly employed in orthopaedic practice and reported results suggest it does reduce allogeneic transfusion rates. A meta-analysis by Huet et al [30] showed a relative risk reduction of 0.35 for the need for allogeneic transfusion with re-infusion drains. Zacharopoulos performed a prospective randomized controlled trial with reinfusion drains, leading to a decrease in allogenic blood transfusion [40]. In contrast, Hazarika showed reinfusion drains had no significant benefit with the downside of additional costs [41]. Reinfusion drains carry the potential for transfusion reactions as the unwashed blood contains fibrin degradation products and other potential contaminants [42,43]. The drained blood needs to be reinfused with 6 hours of commencement to avoid the potential for haemolysis.

A logical strategy in blood conservation is to enhance haemostasis during the peri-operative period. Recently a multitude of publications have highlighted the use and benefits of antifibrinolytic agents. Tranexamic acid (TXA) is one such agent being a synthetic plasminogen-activator inhibitor, showing both clinical efficacy and an acceptable safety profile. TXA inhibits the activation of plasminogen to plasmin by blocking the lysine binding sites of plasminogen to fibrin. This results in a decrease in proteolytic action on fibrin monomers and fibrinogen, leading to clot stabilization [44]. The use of TXA in primary THA and TKA patients has been associated with reduced transfusion rates, increase discharge rate to home, and reduced costs [45].

Tranexamic acid has the desirable features of ease of administration, minimal effect on operative procedure flow, and extremely low cost as a generic medicine. Intravenous TXA has been demonstrated to significantly reduce the amount of blood loss and blood transfusion requirements without an increase in venous thromboembolic risk in multiple studies for both THA and TKA [46,47,48]. Oral TXA has also shown similar effectiveness in orthopadic surgery [49]. Several contra-indications preclude the use of intravenous TXA at the time of surgery, including renal insufficiency, history of previous deep venous thrombosis, cerebrovascular and cardiac disease. One study reported 28% of patients were contraindicated to intravenous TXA [50] and in these patients topical administration nay be more appropriate due to the delay in systemic absorption after application into a joint. Intra-articular application limits systemic exposure and maximizes drug concentration and activity directly at the site of bleeding. Wong et al proved the efficacy of intra-articular TXA in a double-blind, placebo-controlled randomized trial in TKA [51]. The authors demonstrated a significant difference in Hb reduction and blood loss using 3.0g of TXA in 100mls of normal saline compared to placebo, with no difference in thrombo-embolic complications. Plasma levels of TXA

following topical administration were 70% less than an equivalent dose of intravenous injection. More recently, a retrospective study found intra-articular and pericapsular injection of TXA after capsular closure resulted in a transfusion rate reduction from 17.5% to 5.5% as well as a significantly higher post-operative Hb in the TXA group [45]. Alshryda et al performed a systematic review and meta-analysis showing topical TXA to significantly reduce the rate of blood transfusion in both THA and TKA and was safe [52]. Indirect comparison of placebo-controlled trials indicated topical administration to be superior to the intravenous route.

There is however no clear consensus on ideal dosage, timing, frequency and routes for administration of TXA in joint arthroplasty surgery. Additionally there may be differences in the efficacy and response of different regimes between THA and TKA. A number of studies have now compared intravenous TXA with topical TXA demonstrating the efficacy and safety of topical administration in TKA [53,54,55]. Both Patel at al [50], using a single intravenous dose and Soni et al [56], using a 3 dose intravenous regimen concluded topical TXA had similar efficacy to intravenous TXA in terms of perioperative change in haemaglobin, lowest postoperative haemoglobin, total drain output and transfusion rate, together with no increase in complications in randomized prospective studies. In a study comparing 3 methods of administration in TKA, single dose intravenous TXA was more effective than topical and intra-articular TXA injected via the drain in reducing Hb drop [57]. Local administration through the drain yielded least blood drainage post-operatively compared to intravenous and topical application, with 80% reduction drainage volume compared to 45% and 18% respectively. In contrast, Maniar et al found single intravenous dose did not give effective results [58]. A 3-dose regimen of pre, intra and post-op doses of 10mg/kg produced maximum effective reduction of drain loss and total blood loss in TKA. The authors concluded a pre-operative dose prior to tourniquet inflation was important to inhibit the activation of the fibrinolysis cascade.

There are fewer studies examining the utility of topical TXA in THA. Wind et al showed a significant reduction in transfusion rate with intravenous TXA in THA but not with topical TXA [59]. Alshryda et al in contrast published a significant reduction in rate of transfusion with topical TXA in THA, comparable to that achieved with TKA [60]. Studies from Konig et al and Tuttle et al both revealed topical TXA to be efficacious in THA as well [45,61].

Another form of pharmacotherapy used to reduce blood loss is topical fibrin sealant. These agents are composed of fibrinogen and thrombin, which when mixed together during the application process, mimic the final step of the coagulation cascade. Randelli performed a randomized trial of topical fibrin versus a control group but found no difference in Hb levels, postoperative decrease in Hb, drainage or mean total blood loss [62]. In particular, the transfusion rate was 32.3% in the control group compared with 25.8% in the fibrin group and this was not significantly different. The authors concluded the topical application of fibrin sealant was not effective in reducing peri-operative blood loss in total knee arthroplasty. Another randomized study comparing topical fibrin spray to intravenous TXA demonstrated comparable reduction in blood loss but the cost of the fibrin spray was significantly greater [63].

Conclusions

A blood management strategy in total joint arthroplasty aims to reduce the need for allogenic blood and avoid the risks of transfusion, whilst at the same time maximizing haemaglobin level and preventing anaemia in the acute post-operative period. Effective blood conservation encompasses pre-operative identification of patients at high risk for transfusion, correcting pre-operative anaemia with haemopoietic agents, salvaging blood lost during the perioperative period, limiting post-operative blood loss with haemostatic measures and individualizing the transfusion trigger according to the patient's symptoms and medical co-morbidities. The algorithm used in our unit is shown in figure 1. A proactive approach to blood management will lead to a positive effect on early and long-term outcomes and greater success in care of the joint arthroplasty patient.

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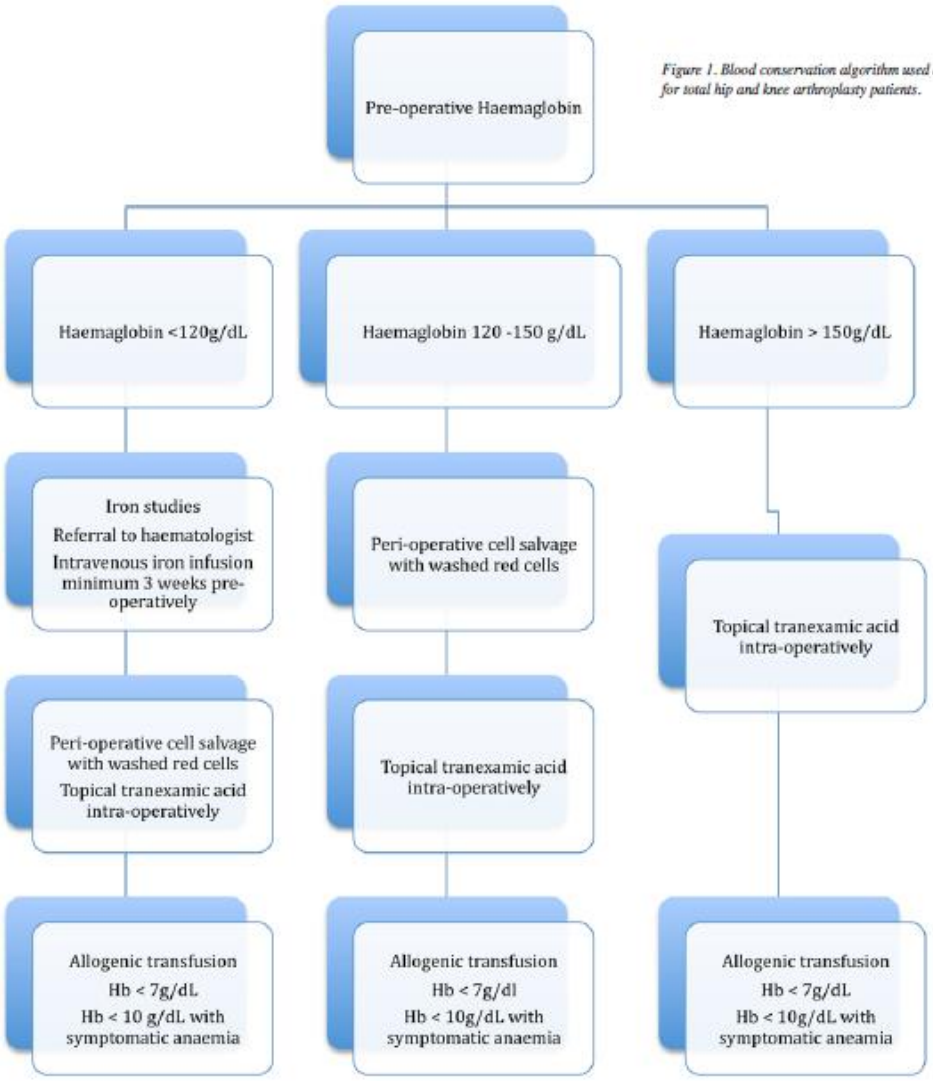

Figure 1. Blood conservation algorithm used at our institution for total hip and knee arthroplasty patients.

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